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The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review

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The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review

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NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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List of abbreviations

2D	two dimensional
3D	three dimensional
α	flip angle (in MRI sequence)
BIDS	Bath Information and Data Services
CE	contrast enhanced*
CI	confidence interval
CT	computed tomography
DSA	digital subtraction angiography
ECST	European Carotid Surgery Trial
FISP	fast imaging with steady-state precession (MRI sequence)
FN	number of positive cases incorrectly identified as negative by test*
FP	number of negative cases incorrectly identified as positive by test*
Gd	gadolinium
IOA	intraoperative arteriography*
ln	natural logarithm
LR–	likelihood ratio of a negative test result*
LR+	likelihood ratio of a positive test result*
MR	magnetic resonance*
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NA	not applicable*
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NPV	negative predictive value*
NR	not reported in article*
PPV	positive predictive value*
PTA	percutaneous transluminal angioplasty*
Q^*	maximal joint sensitivity and specificity
QALY	quality-adjusted life-year
ROC	receiver operating characteristic
SCTA	spiral computed tomography angiography
SROC	summary receiver operating characteristic
TE	echo time (in MRI sequence)*
TIA	transient ischaemic attack*
TN	number of negative cases correctly identified as negative by test*
TOF	time of flight
TONE	tilted optimised non-saturating excitation
TP	number of positive cases correctly identified as positive by test*
TR	repetition time (in MRI sequence)*

* Used only in figures and tables

Executive summary

Background

The principal manifestations of carotid and peripheral atherosclerosis, respectively, include transient ischaemic attack and stroke, and lower limb arterio-occlusive disease resulting in intermittent claudication (pain on walking), ischaemic rest pain, ulceration or gangrene. The total costs to the NHS of arterial and venous disease, in hospital and primary care, exceed £350 million; the total costs of stroke have been estimated as substantially higher, at 5.8% of total expenditure.

Clinical decision-making relies on evaluation of the vessels in terms of the degree of stenosis, or narrowing. Magnetic resonance angiography (MRA) is a technique for imaging blood vessels that contain flowing blood. It can be performed on most magnetic resonance scanners installed in hospitals today, and represents an alternative to conventional angiographic techniques using X-rays (digital subtraction angiography (DSA)), or more recent imaging developments, including ultrasound. In this review the use of contrast-enhanced MRA and two-dimensional (2D) and three-dimensional (3D) time-of-flight (TOF) MRA for presurgical assessment in carotid artery disease and in peripheral vascular disease is considered.

Objectives

- To identify the literature on MRA that is relevant to the use of MRA for presurgical assessment in carotid artery disease and in peripheral vascular disease.
- To synthesise published evidence about the diagnostic performance of MRA, compared with DSA, in carotid artery disease and in peripheral vascular disease at surgical decision thresholds.
- To use this evidence, together with other information about costs and outcomes, to model the cost-effectiveness of MRA compared with conventional angiography in carotid artery disease and in peripheral vascular disease.

Methods

Data sources

- Electronic searches of MEDLINE, EMBASE, HealthSTAR, Science Citation Index, Index to Scientific and Technical Proceedings, the Cochrane Library, Inside from the British Library, EconLIT, HEED, the NHS EED and the Online Computer Library Centre, 1990–1999.
- A limited Internet search for reviews, 1990–1999.
- A handsearch of ten key journals and the Department of Health databases (Hospital Episode Statistics and Health Related Resource Groups), 1990–1999.

Study selection

Studies of the diagnostic performance of MRA in the relevant clinical conditions and performed on humans were included with two provisos: that sufficient data were reported for the construction of a 2 × 2 contingency table, and that application-specific inclusion criteria were satisfied. Non-English-language studies were included. Studies reporting cost data were included, providing resource use and costs for the UK setting were reported separately, and providing the study did not use expert opinion or charge data to estimate costs.

Data extraction

Checklists that covered study design, patient characteristics, technical details and potential biases in study execution were completed independently by two reviewers. Consensus was reached on any disagreements. One reviewer, who worked with another where difficulty arose, extracted results on diagnostic performance. Summaries were written to describe each article. Cost data were extracted and summarised by two team members.

Data synthesis

Summary receiver operating characteristic methods were used to combine the results of diagnostic performance studies, grouped by MRA technique and diagnostic threshold. The thresholds used were:

- For carotid artery disease, using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) protocol:
  - 0–69% or 100% versus 70–99%
  - 0–49% or 100% versus 50–99%
  - 0–99% versus 100%.
- For peripheral vascular disease:
  - 0–49% versus 50–100%
  - 0–49% or 100% versus 50–99%
  - 0–99% versus 100%.

Study validity was investigated using a multiple linear regression analysis. Overall event rates were calculated by pooling patient results from the included studies. A decision analytic model was used to combine information from the literature and cost estimates, in order to determine the relative cost-effectiveness of MRA and DSA in the two clinical applications. The analysis was performed from the perspectives of the healthcare purchaser and clinician. Sensitivity analysis was performed.

Results

Ten articles on carotid artery stenosis satisfied all the inclusion criteria and a further 24 satisfied at least four inclusion criteria. There were too few articles on the latest contrast-enhanced techniques for quantitative synthesis, but the results appear better than those for 2D and 3D TOF methods. The TOF methods are highly accurate for detecting occlusion and 70–99% stenoses, but are less accurate for 50–99% stenoses. The decision analytic model showed that over 10 years following its use, MRA is expected to cost £194 less than DSA, with no difference in expected quality-adjusted life-years (QALYs). Providing the equipment is used at more than 10% of capacity, MRA is associated with lower expected costs than DSA.

Twenty articles on peripheral vascular disease satisfied all the inclusion criteria. Both 2D TOF and contrast-enhanced MRA are highly accurate for distinguishing 0–49% from 50–100% stenoses. The contrast-enhanced techniques show a non-significant trend for improved performance over 2D TOF MRA. The decision analytic model showed that there is no difference in expected QALYs for MRA and DSA. If the equipment is used at under 100% of capacity, 2D TOF MRA is associated with higher expected costs than DSA, but contrast-enhanced MRA has lower expected costs.

Conclusions

Implications for healthcare

In carotid artery disease, 2D and 3D TOF MRA techniques are accurate for identifying both occlusions and 70–99% stenoses as defined by conventional angiography. The evidence does not support their use for identifying 50–99% stenoses. If the utilisation rate for an MRA system to evaluate all patients (with and without carotid artery disease) is greater than 10%, then MRA is likely to be a cost-effective option.

In peripheral vascular disease the evidence supports the use of 2D TOF and contrast-enhanced MRA techniques for identifying occlusions and 50–100% stenoses. If both DSA and MRA are already available in the local setting, then MRA is more cost-effective than DSA, especially if contrast-enhanced MRA is available.

The conclusions about cost-effectiveness are valid only for high-quality diagnostic studies. Such examinations can only be performed following training and adequate experience. Consequently, there is a case for guidelines, training and accreditation schemes to be established by the relevant professional bodies.

Recommendations for further research

- The establishment of a multicentre tracker study to determine the accuracy of contrast-enhanced MRA, duplex ultrasound and computed tomography (CT) angiography (singly or in combination) for the investigation of peripheral vascular disease.
- The establishment of a multicentre tracker study to determine the accuracy of MRA, duplex ultrasound and CT angiography (singly or in combination) for the investigation of carotid artery disease.
- Support for data from primary studies to be held on web servers is recommended, as it would facilitate future modelling activity.
- A rapid, structured review focused on contrast-enhanced MRA in 2002.
- The compilation of general guidelines for designing and presenting trials of diagnostic and imaging technologies.
- A methodological investigation of publication bias specifically focused on diagnostic literature.
- Studies on patient preferences for the diagnostic process and expected impact on their health status and health-related quality of life.

- Monitoring of expert opinion to ensure that trials of new non-invasive MRA techniques are implemented in a timely way.
- Updating of the peripheral vascular disease model in 2005.

Chapter 1
Background

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is a technique for imaging blood vessels that contain flowing blood. It can be performed on most magnetic resonance scanners installed in hospitals today, and represents an alternative to conventional angiographic techniques using X-rays, or more recent imaging developments, including ultrasound. The aim of all imaging methods is to estimate the degree of stenosis, or narrowing, of the vessel that is being evaluated.

The most commonly used MRA methods are termed time-of-flight (TOF) techniques and are non-invasive. Contrast is generated by use of a gradient-echo pulse sequence, which shows flowing blood as a high signal. Use of relatively short repetition times results in a marked reduction in the signal from stationary tissues ('background') due to saturation effects. A high intravascular signal is generated by continuous inflow of fully relaxed protons from outside the imaging volume, resulting in replenishment of protons already within the imaging volume, which have lost some of their signal due to the fact that they experience successive radiofrequency pulses. In order to ensure inflow of a sufficient number of protons into the imaging slice, the repetition time must be tailored to the velocity of blood flow. Typically, values of more than 30 ms must be used for optimal effect when performing arteriography. The choice of scan plane is crucial, as maximal inflow is experienced when the imaging slice is orthogonal to the direction of flow in the vessel. A short echo time must be also used to minimise intravoxel dephasing. Multiple projections of the vascular structure are generated, usually with a maximum intensity projection algorithm, and this provides visualisation analogous to that of conventional angiographic techniques. However, imaging artefacts mean that the degree of stenosis may be overestimated in TOF techniques. Two-dimensional (2D) imaging involves sequential acquisition of thin slices (1.5 mm) over the volume of interest. The method is fast, relatively insensitive to patient movement, and useful for a wide range of flow velocities. The spatial resolution is relatively poor and the method is prone to artefact when flow is complex. Three-dimensional (3D) imaging has higher spatial resolution, is faster than the 2D method and is less prone to artefact from complex flow, but is less sensitive to slow-flowing blood.

Gadolinium (Gd) contrast-enhanced imaging has recently been introduced and, although the technique is more invasive, the use of Gd means that a much greater volume of the body may be imaged in a short period of time. There can be a 20-fold time advantage in using contrast-enhanced rather than TOF methods.

The final MRA technique is phase-contrast imaging. This provides quantification of flow in vessels. A computer-subtracted image is calculated showing the net accumulated phase from flowing blood. Phase contrast is used much less in clinical practice than the other methods owing to the long acquisition and post-processing times, and even greater problems with artefacts than for the TOF methods. Furthermore, sensitivity to turbulent flow again leads to overestimation of the degree of stenosis.

As the techniques are developed, there are likely to be improvements in terms of higher signal-to-noise ratio or improved spatial resolution. However, although such changes may enhance physician confidence, it cannot be assumed that they lead to an increase in diagnostic accuracy or improved outcome for the patient.

Since MRA techniques are constantly evolving, this makes the timing of evaluation problematic: definitive results from trials are likely to have been obtained on superseded equipment, thus confounding decisions about new purchases. This is a feature common to most fields where the health technology is in rapid development, resulting in a lack of evidence about the impact of the technology on outcome for the patient and on economic issues. This may be because insufficient time has passed for conclusions to be drawn, or because large, reliable studies cannot be performed as the technology is continually improved. In these situations the technique of decision analytic modelling is increasingly being used as an adjunct to the conventional systematic literature review.[1,2] Modelling offers a solution, as it allows the effects of changes in the

performance of a test to be tested in advance of results from lengthy trials. The aim of the present study was to synthesise available evidence about the use of MRA in the clinical conditions outlined below, and to use decision analytic modelling to draw conclusions where evidence is sparse. An introduction to modelling is presented later in this chapter.

Clinical background

Atherosclerosis is one of the most prevalent disorders affecting Western society, and is almost ubiquitous after the age of 40 years. Its principal manifestations, apart from coronary artery disease, include transient ischaemic attack, stroke and lower limb arterio-occlusive disease, resulting in intermittent claudication (pain on walking), ischaemic rest pain, ulceration or gangrene. The total costs to the NHS in 1992–93 of arterial and venous disease were £317 million (hospital) and £46 million (primary care). The total costs of stroke to the NHS and social services has been estimated as substantially higher at £2318 million, or 5.8% of total expenditure.[3] Such figures have led some observers to predict that by the year 2020 the cumulative cost of managing complications of atherosclerosis and cancer will be identical. Before clinical decision-making can progress along appropriate lines for patients presenting with transient ischaemic attack, stroke or lower limb claudication, it is essential that several questions are answered correctly regarding the presence, distribution and severity of arterial lesions. For both the carotid and peripheral circulation, the investigative modality perceived as being most accurate is catheter angiography. However, this test is costly, invasive and unpleasant for the patient. If this test was used indiscriminately the cost of investigation would be prohibitive, while in the case of suspected carotid disease the procedure itself carries a risk of stroke (0.5–4%),[4–7] thus diminishing the overall benefit of surgical intervention in those patients who need treatment. Investigation for both carotid disease and peripheral vascular disease is designed to divide patients into candidates for medical or surgical intervention, but the approach is different in the two cases. In carotid disease measurement of the severity of the lesion around the carotid bifurcation is of vital importance, while in peripheral vascular disease questions of location and distribution are more relevant. For this reason the two diseases are discussed separately.

Carotid disease

In patients presenting with transient ischaemic attack or stroke, as many as 50% of cases are due to artery-to-artery embolism, of which the majority are thought to originate from the internal carotid artery. Clinically, nothing distinguishes a stroke due to an internal carotid artery embolism from that due to embolism from other sites. The critical information required from imaging of the carotid bifurcation is the degree of narrowing, as it is known from large randomised trials[8–10] that the risk of stroke is related to the degree of stenosis. The protocols used to measure carotid stenosis were different in the two trials, although both used the angiographic view showing the point of maximum narrowing to calculate the numerator. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) the denominator was the diameter of the distal internal carotid artery where the sides are parallel. In the European Carotid Surgery Trial (ECST) method, the denominator was the estimate of the original width of the artery at the widest part of the bulb, bearing in mind the slight widening of the normal origin of the internal carotid artery.

Although both the NASCET and ECST trials reported significant benefit from carotid endarterectomy for patients with a stenosis of 70–99%, the different methods of determining the percentage stenosis require careful consideration. There are two published articles comparing measurements made by the two protocols,[11,12] which indicate that a 70% stenosis measured by the NASCET method would be equivalent to an 82% stenosis using the ECST method. Conversely, a 70% stenosis in the ECST study would have been measured at 50% by the NASCET investigators. Thus, although both studies recommend surgery for stenosis of greater than 70%, but not for occlusions (100% stenosis) where endarterectomy is technically impossible, the influence of the measuring technique should be borne in mind.

For clarity, we record here the method used to determine the degree of stenosis in each study included in the review. However, the quantitative analyses were done using only results from studies that used the NASCET protocol. We considered three different diagnostic thresholds, all of which are based on the NASCET protocol of measurement.

These trials[8,9] found a clear benefit of surgery in patients with symptomatic stenoses of 70–99%

measured by conventional angiography using the NASCET criteria. We therefore evaluated the evidence on the diagnostic performance of MRA against conventional angiography at this threshold. NASCET and ECST found a smaller benefit of surgery for patients with symptomatic 50–99% stenosis, with ECST[9] also demonstrating a clear downward trend in the benefit of surgery for stenoses less than 70–99% (measured by the NASCET protocol). The benefit in this group was also dependent on the age and sex of patients. However, a recent Cochrane Review[13] concluded that there was a benefit of surgery for patients with 50–69% stenosis, so we have also evaluated the evidence on the diagnostic performance of MRA for these more moderate stenoses (i.e. for patients with 50–99% stenosis). Finally, the ability of the technique to distinguish patent from occluded vessels was also assessed.

For imaging the carotid circulation the most important issue is the ability of an imaging test to define accurately the degree of stenosis. Ideally, the test should also be able to identify the presence of a tandem lesion, which is a second co-existent lesion remote from the primary site of narrowing at the origin of the internal carotid artery. Patients with such stenoses were excluded from the NASCET trial.[8] Where such a stenosis is inoperable, and of a greater degree of stenosis than the first lesion, surgery may be contra-indicated. Otherwise, appropriate measures to treat this second lesion or minimise its effects can be instituted. The major significance of a tandem lesion lies in its contribution to poor outcome in cases where it remains occult, although there is disagreement between practitioners about the importance of such lesions.[14,15]

The candidate imaging tests for determining the degree of stenosis in carotid disease are X-ray arteriography (often in the form of digital subtraction angiography (DSA)), duplex ultrasound, spiral computed tomography angiography (SCTA) and MRA.

X-ray arteriography (DSA)

X-ray arteriography involving the injection of iodinated contrast material can be performed in the conventional way, resulting in images on film. More commonly, intra-arterial digital subtraction techniques are used that allow the subtraction of non-enhancing parts of the image. The result may be viewed on a computer monitor or reproduced on film. X-ray arteriography is considered the gold standard or definitive test against which other tests must be judged, since it has high spatial resolution and can be used to assess tandem lesions. However, it is an invasive test, carrying a risk of stroke of up to a 4%.[4–7] Furthermore, it is less suitable for the elderly and frail.[16] By following practice guidelines, other authors have reported a substantially lower complication rate (e.g. 0.09% for permanent neurological complications[17]). If criteria for reporting the result other than the NASCET and ECST criteria are used, this can lead to different decisions on management.[18] In addition to the high costs of contrast agent, catheters and guidewires, an overnight hospital stay may be required, which adds to the cost of the intervention.[19–21] In the Leeds Teaching Hospitals NHS Trust, for example, this adds approximately £300 per patient. Although both the risk and the cost may be reduced by using intravenous DSA this technique may not provide such good visualisation of the carotid vessels.[22]

Despite its position as the most trusted test, inter- and intra-observer variations in assessing conventional angiograms occur which may result in inappropriate patient management. For example, Young and co-workers[23] quote inter-observer variability of 9% and intra-observer variability of 6%.

Duplex ultrasonography

In contrast, Duplex ultrasonography is non-invasive and is performed on an outpatient basis. Thus the technique is inexpensive and the technology is readily available in the majority of centres. Ultrasonography may be repeated at no risk to the patient, and in experienced hands a sensitivity and specificity above 90% can be expected.[24] However, there is strong operator dependence, with the potential for misinterpretation where the necessary expertise is lacking. The method cannot be used to assess tandem lesions and it may be difficult to distinguish high-grade stenosis from occlusion, which is important in selecting patients for surgery. The criteria for measuring the degree of stenosis are under debate,[25–27] with very different results found in different laboratories.[28]

SCTA

Like conventional angiography, SCTA has the disadvantages of ionising radiation and iodinated contrast material. It is sometimes advocated as an alternative to MRA because of its speed, particularly when a large field is to be imaged (e.g. from aortic arch to the intracranial circulation). Furthermore, it may be associated with superior spatial resolution.[29]

MRA

The TOF and phase-contrast methods initially used for MRA are non-invasive. Although the more recent contrast-enhanced techniques which require venous access are invasive, they are less so than conventional angiography. Contraindications to MRA are those that apply to magnetic resonance imaging (MRI) in general, and include pacemaker, ferromagnetic aneurysm clips, intra-orbital metallic foreign body and a small number of specific implanted medical devices. It is said that MRA performs similarly to DSA in the detection of stenoses, especially at the carotid bifurcation,[24] with a sensitivity and specificity of 80–100%. However, a systematic review published in 1994[30] noted that the published studies were not comparable and usually involved small patient numbers that were non-uniformly selected.

Unlike ultrasound, assessment of tandem lesions is possible with MRA, but there are few data in the literature on the topic. Areas where tandem lesions may occur are hard to image using MRA. For example, artefacts leading to signal loss occur near the carotid syphon, and signal loss can result when there is turbulent flow in the intracavernous internal carotid artery.[31]

Currently, MRA is limited to specialist centres, although diffusion of the technique to district general hospitals is likely. The drawbacks associated with MRA include problems with overestimation of the degree of stenosis caused by artefacts and poor spatial resolution. Like ultrasonography, MRA can be performed as an outpatient procedure, but the costs are considerably higher than for ultrasound.[19] These issues were investigated in this review. A full investigation of the alternative modalities was beyond the scope of this review, but the issue is discussed further in chapter 8.

Peripheral vascular disease

Peripheral vascular disease differs from carotid disease in that imaging must be performed over a large region of interest, from the abdominal aorta to the foot. For peripheral vascular disease, assessment of the exact degree of stenosis is not as critical as the distribution of disease, although it is desirable to be able to distinguish occlusion from stenosis. Patients with short occlusions and stenoses can be treated with angioplasty, while more extensive disease may require surgical reconstruction. The success of a surgical bypass procedure is dependent on satisfactory inflow from normal or minimally diseased proximal vessels and a patent distal circulation. The length and type of graft material may also influence outcome.

Assessment of disease may be reported in a number of ways:

- over the whole of the vascular tree
- aortoiliac segment
- femoropopliteal segment between groin and knee
- infrapopliteal segment below knee
- distal (crural) vessels.

Once a full road map of the arterial supply has been obtained, potential therapeutic measures can be considered. These include transluminal angioplasty, endovascular stenting, endarterectomy, reconstructive surgery or a combination of two or more of these techniques. In patients with critical limb ischaemia (rest pain, ulceration, gangrene) amputation may be required if revascularisation is deemed impossible following vascular imaging.

In this review, we considered three diagnostic thresholds, which were chosen as they represent clearly defined differences in the severity of disease, and are accepted clinical practice for grading and interventional treatment management: 0–49% versus 50–100%; 0–49% or 100% versus 50–99%; and 0–99% versus 100%.

The same candidate imaging tests as for carotid disease are relevant here, and the same considerations of cost, availability, expertise and safety apply. Their relative merits for the assessment of peripheral vascular disease are slightly different than for the assessment of carotid disease.

X-ray arteriography (intravenous or intra-arterial DSA)

As for carotid disease, this technique is regarded as the gold standard in peripheral vascular disease and is the one against which others must be judged. Contrast injection may be intravenous or intra-arterial. The method has extremely high spatial resolution, but may have poor performance, particularly when using an intravenous technique for demonstrating patent distal vessels, owing to dilution of the contrast medium and difficulties with the timing of data acquisition. This problem may be exacerbated in patients with proximal occlusions, and these potential shortcomings may have an important effect on patient management.

A further drawback to conventional angiography (which applies to the investigation of both carotid

disease and peripheral vascular disease) are the risks of deteriorating renal function in patients with pre-existing renal impairment. This is related to the volume of iodinated contrast agent that is used, since these agents are potentially nephrotoxic. Certain newer agents are claimed to have reduced nephrotoxicity and, although expensive, their use may be justified in such patients. MRA is considered to be an important mode of investigation in patients at particular risk of renal complication.[32] A further rare complication of conventional angiography is the development of lactic acidosis in diabetic patients receiving metformin.

Duplex ultrasound

Duplex ultrasonography is more reliable for assessing femoropopliteal disease than aortoiliac disease. Assessment of the latter may be hampered by bowel gas. Furthermore, Koelemay and co-workers[33] found it to be less accurate for the distal circulation below the knee. Unlike MRA and conventional angiography, duplex ultrasound does not provide a road map of the circulation, but may be useful in distinguishing patients suitable for endovascular procedures from those likely to require surgical reconstruction.

SCTA

The main role for SCTA in patients with vascular disease is in the assessment of the aortoiliac segment in patients with aneurysmal disease. Its use in the assessment of peripheral vascular disease is relatively uncommon in view of the extensive field size required to image the lower limb vascular supply and the small diameter of the distal (below knee) vessels. Thus there is little published evidence about the technique, but the introduction of multislice computed tomography (CT) may hasten the development of reliable vascular imaging protocols.

MRA

The TOF methods are non-invasive, and unlike ultrasound can be used to image distal segments.[34] With contrast enhancement it is possible to visualise patent distal segments not seen using either X-ray arteriography or TOF methods, the longer imaging time allowing filling by collaterals to be visualised.[35] MRA methods have a high cost associated with the long examination times. For example, a comprehensive TOF evaluation from lower aorta to ankles requires 400 axial images and a total examination period of 90 minutes. Although contrast-enhanced moving-table MRA[36,37] allows comprehensive evaluation over the same region within 30 minutes, the reduction in time is balanced by the cost of the additional contrast medium required (30 ml of Gd by intravenous injection).

Effectiveness of diagnostic devices

There is clearly a complex combination of costs, risks and benefits to be considered when determining the cost-effectiveness of the assessment techniques. The evaluative framework proposed by Fineberg and co-workers[38] and others[39,40] is valuable when considering the effectiveness of diagnostic devices. The levels of the hierarchy are:

- technical performance
- diagnostic performance
- diagnostic impact
- therapeutic impact
- patient outcome
- health economic impacts.

The most appropriate study design to investigate performance at each level was outlined in an earlier review,[41] and is discussed by Deeks.[42] By considering the levels separately it is much easier to classify articles and discuss their findings. In terms of dissemination, the results of a review can be made more accessible to different healthcare professionals and consumers, who seek evidence of effectiveness at different levels of the hierarchy. The hierarchy is applicable even when an imaging device is being used for purposes other than diagnosis, because the higher levels may be considered independently from the lower ones. At the level of diagnostic performance, it is helpful to define a dichotomy that allows the classification of patients into one of two groups, which can be compared with the equivalent reference standard result. The division is different for the two clinical scenarios. In this review, for carotid disease the diagnosis of a surgically significant stenosis (> 70%), a 50% stenosis or a total occlusion was considered, while for peripheral vascular disease, although the decision to proceed with surgery is multifactorial, the diagnostic threshold is a ≥ 50% stenosis or total occlusion. We also sought evidence at other levels of the hierarchy to help in determining the cost-effectiveness. Decision analytic modelling was used to supplement published evidence.

Survey

To help us define the questions to be addressed by this review we undertook a survey of vascular surgeons and radiologists in the UK. If the review

were to be viewed purely from the perspective of the purchaser of new equipment, then it would be valid to concentrate on the most recent generation of the technology (i.e. contrast-enhanced MRA). However, to ensure relevance of the review to clinical practitioners we wished to include all generations of technology that are currently clinically relevant. An additional benefit of reviewing earlier generations is that it allows a determination of the incremental cost-effectiveness of each generation.

A questionnaire was sent to 100 UK radiologists and 400 UK vascular surgeons. The questionnaire sought information on MRA techniques currently available to each group. The questionnaire is reproduced in appendix 2. Recipients were also asked to state their preferred technique (assuming availability) for each clinical application (carotid artery stenosis, peripheral vascular disease). To encourage responses, the questionnaire comprised only six questions and was in the form of a single-page letter suitable for return by fax.

Overall, 162/500 (32%) of the questionnaires were returned from 60 radiologists and 102 vascular surgeons. Of the respondents, 142/162 (88%) had MRA available on site (*Figure 1a*), with 85/162 (52%) having access to contrast-enhanced MRA, 96/162 (60%) to 3D TOF MRA and 108/162 (63%) to 2D TOF MRA. The field strengths of these systems are shown in *Figure 1b*.

In total, 77/162 (48%) respondents currently used MRA in the assessment of carotid artery stenosis and gave details of the methods used. Of these, 26/77 (34%) used contrast-enhanced MRA, 32/77 (42%) used 3D TOF and 47/77 (61%) used 2D TOF (*Figure 2a*). In total, 35/162 (22%) respondents currently used MRA in the assessment of peripheral vascular disease and gave details of the methods used. Of these 22/35 (63%) used contrast-enhanced MRA, 4/35 (11%) used 3D TOF and 15/35 (43%) used 2D TOF (*Figure 2b*).

Of the responding radiologists, 51/60 (85%) answered the question about their method of choice if all methods were equally available: 49/51 (96%) said they would use MRA for the evaluation of carotid artery stenosis, and of these 32/49 (65%) would choose contrast-enhanced MRA (*Figure 3*). Of the responding surgeons, 77/102 (75%) answered the question about their method of choice if all methods were equally available: 37/77 (49%) would use MRA for the evaluation of carotid artery stenosis, and 28/37 (76%) of these would choose contrast-enhanced MRA (*Figure 3*).

Of the responding radiologists, 51/60 answered the question about their method of choice if all methods were equally available: 39/51 (87%) of these would use MRA for the evaluation of peripheral vascular disease, and 36/39 (92%) of these would choose contrast-enhanced MRA

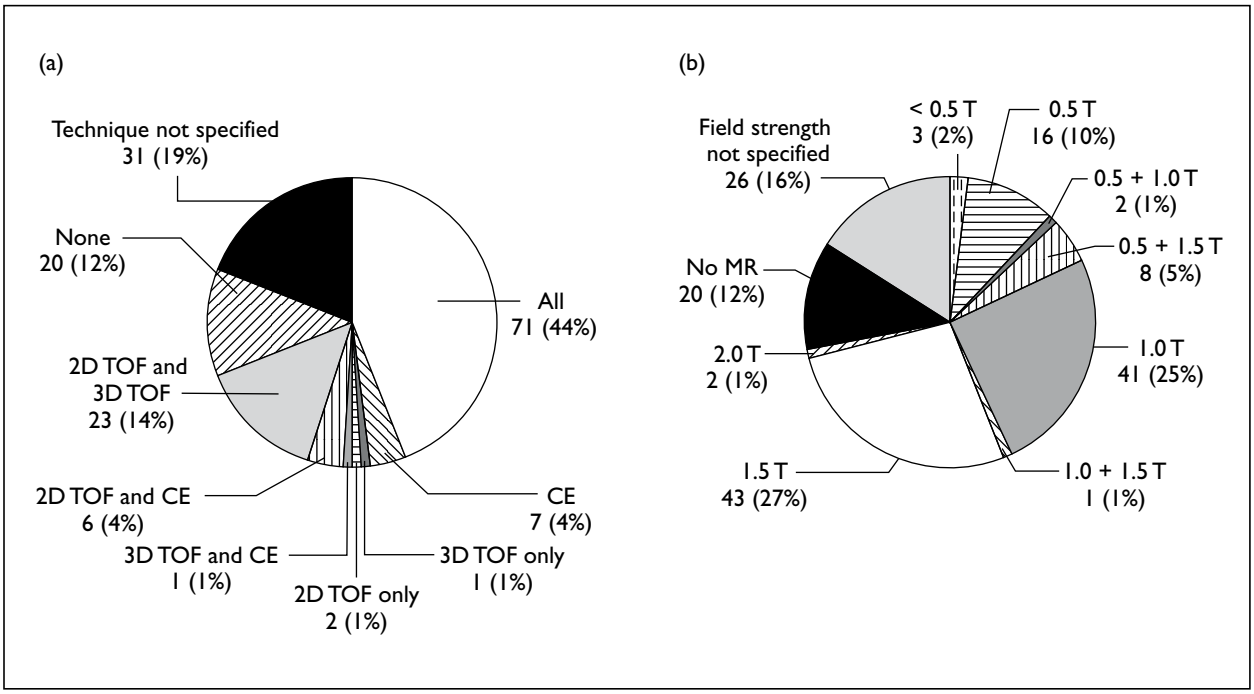

FIGURE 1 *Technologies (a) and field strengths (b) available to questionnaire respondents (n = 162). CE, contrast enhanced; MR, magnetic resonance*

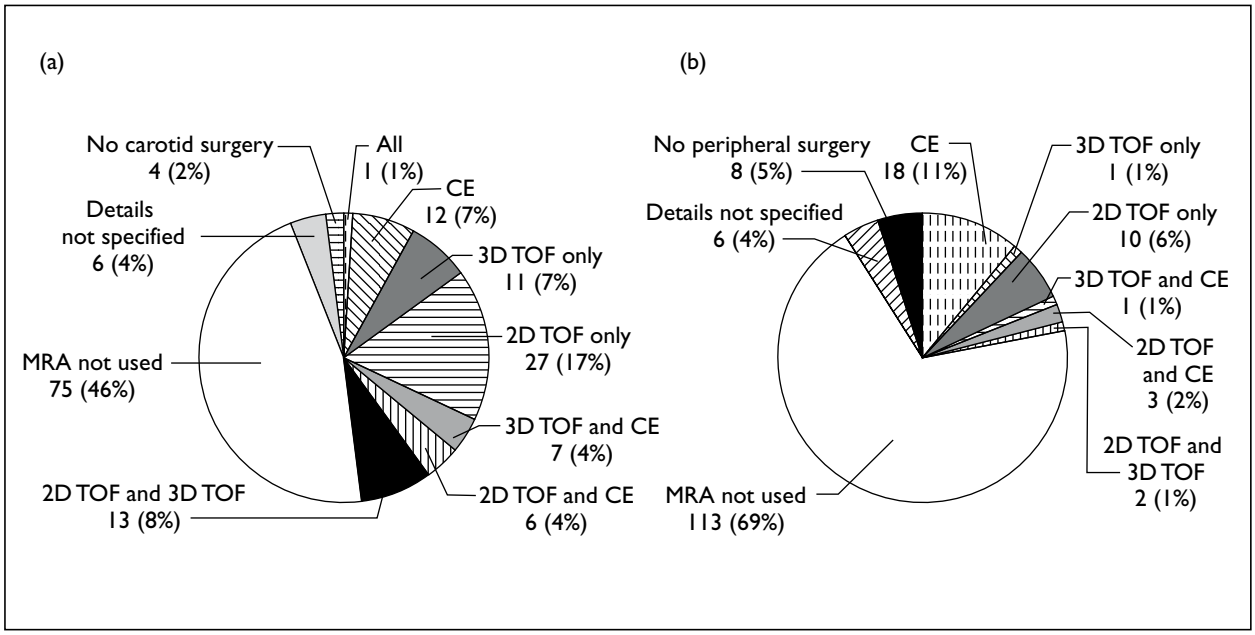

FIGURE 2 *MRA methods currently used for carotid assessment (a) and peripheral vascular disease assessment (b) (*n *= 162)*

(*Figure 4*). Of the responding surgeons, 75/102 (74%) answered the question about their method of choice if all methods were equally available: 41/75 (55%) would use MRA for the evaluation of peripheral vascular disease, and 40/41 (98%) of these would choose contrast-enhanced MRA (*Figure 4*).

The response from surgeons was lower than the response from radiologists, presumably

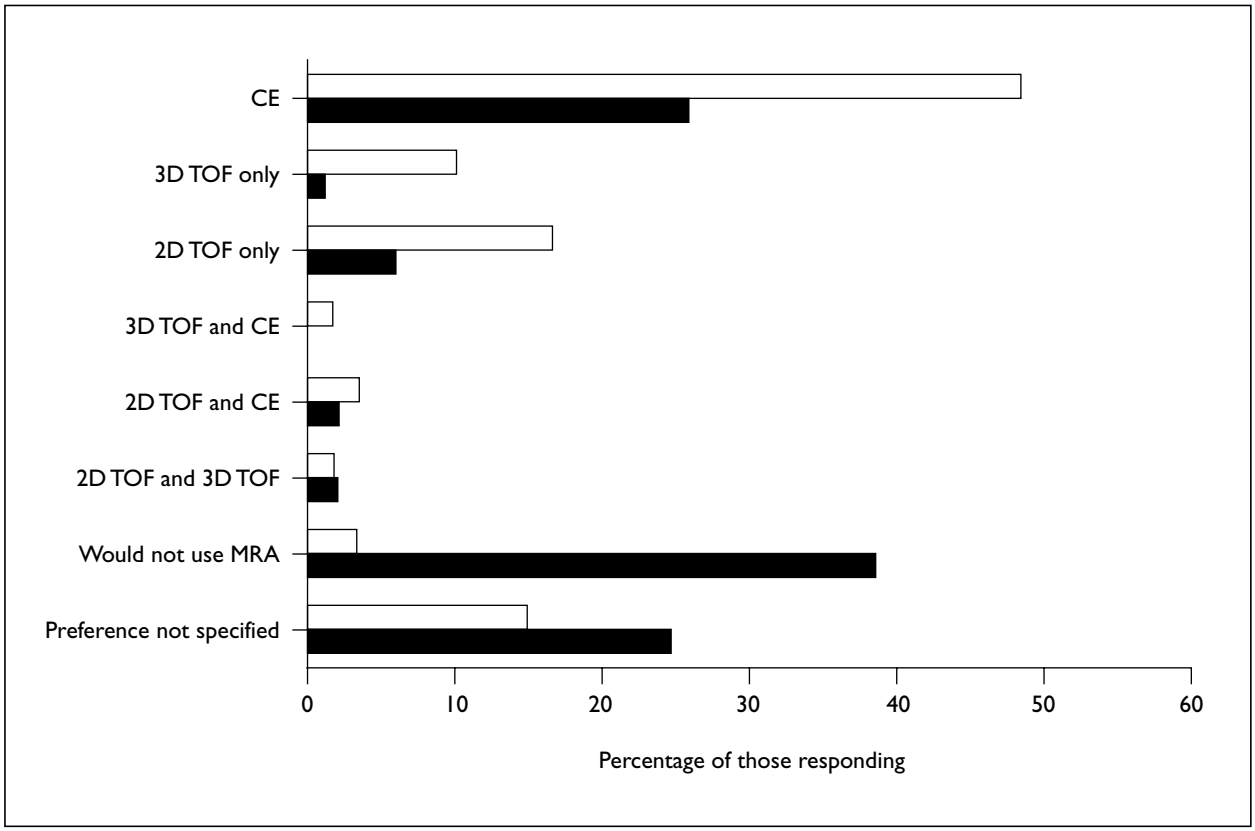

FIGURE 3 *Radiologists' (*n *= 60) and vascular surgeons' (*n *= 102) preferences (if technology were available) for carotid assessment (□, Radiologists; ■, vascular surgeons)*

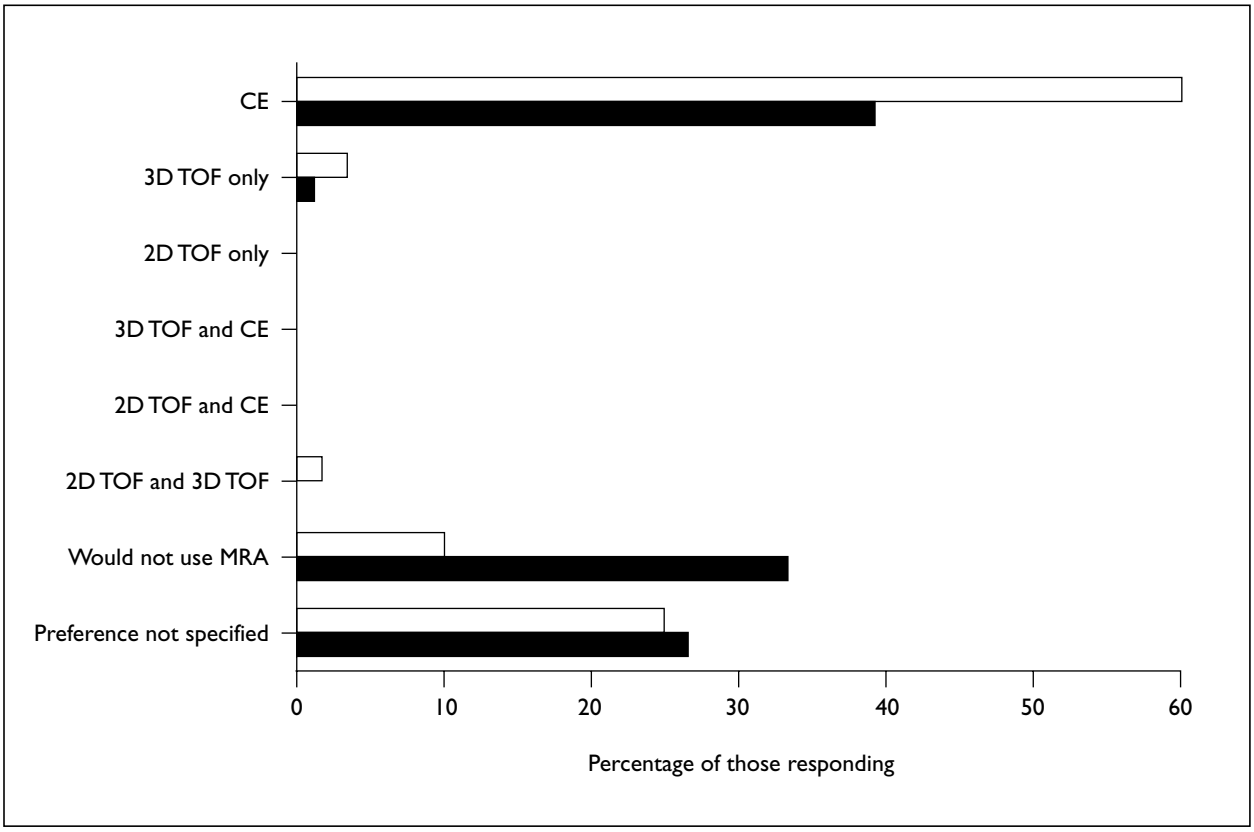

FIGURE 4 *Radiologists' (n = 60) and vascular surgeons' (n = 102) preferences (if technology were available) for peripheral vascular disease assessment (□, Radiologists; ■, vascular surgeons)*

because of the radiological nature of some of the questions. We are also aware that several questionnaires sent to surgeons were passed on to radiologists who should also have received one of their own.

The survey results led to a decision to include 2D TOF, 3D TOF and contrast-enhanced MRA methods in the review. They also indicate that demand for contrast-enhanced MRA capabilities in the future may be higher for the assessment of peripheral vascular disease than for carotid artery stenosis. The findings are further discussed in chapter 8.

Decision analytic modelling

In the presence of growing pressures on health-care budgets the economic analysis of healthcare programmes is acquiring an increasing importance and interest. Evidence on the relative value for money of alternative healthcare treatments is particularly relevant in the case of uncertainties relating to the adoption of new technologies. To validate the implementation of new healthcare interventions policy-makers often perceive the need for an economic evaluation of these potential new therapies.

Our economic evaluation of MRA uses the approach of cost-effectiveness analysis to investigate the costs and outcomes of the alternative diagnostic interventions. We define a 'cost-effectiveness' analysis as a comparison of the costs and health outcomes of different health interventions, without distinguishing whether the key measure of effectiveness is unidimensional (e.g. health-years gained) or if it embodies both health-related quality of life and life expectancy. In this second case, where synthetic indices such as quality-adjusted life-years (QALYs) or healthy-year equivalents are used to evaluate both patients' quality of life and survival rate, it would be more appropriate to define the analysis as a cost–utility analysis.

Decision analysis to synthesise clinical and economic data from a number of sources was used. This provided a flexible and timely framework for the evaluation. Decision analysis models provide a way of combining data from a number of sources and to predict the relative cost-effectiveness of alternative therapies.[43] The

use of decision analysis to model clinical problems and conduct cost-effectiveness analyses has the advantage of reducing large and often complex problems into smaller and more manageable ones. Moreover, they provide an opportunity to supplement missing or incomplete data with assumptions or expert opinion.[44,45] Sensitivity analysis and simulations were used to incorporate uncertainties related to the assumptions undertaken in the construction of the model, the data available and the potential multiple objectives of the investigation.

The choice of a static modelling approach was dictated by the limited availability of data, and was not conceptually the ideal choice. The main drawback of this approach is the assumption that values of variables are constant with time. This is believed not to be a valid assumption for the risk of stroke and death, which decrease with time.[8,9] However, models that do incorporate changes with time, such as Markov models, risk models or regression models, require detailed data for each time point considered. Data this detailed were not available in the literature.

Models can sometimes be the only guidance available to decision-makers, but must be treated with caution, especially when used in place of trials.[46] In the field of medical imaging, the absence of data from good-quality trials in many areas presents opportunities to use modelling to make the best use of the information that is available.

In this review, the primary objective of modelling was to determine the relative cost-effectiveness of MRA compared with conventional angiography. Economics was added to data from studies concentrating on clinical end-points, and the findings of short-term trials were projected over longer periods.

Conclusion

In this chapter, the technology of MRA has been introduced and its potential use in the assessment of carotid and peripheral arterial disease considered as an alternative to other imaging modalities. The simple evaluative framework that facilitates the assessment of imaging technologies has been outlined and the role of decision analytic modelling introduced. In the next chapter, the research questions to be addressed in the review are defined.

Chapter 2

Research questions

This study concerned the use of MRA in two separate clinical scenarios.

Carotid artery disease

The research questions were:

- Compared with the gold standard of intra-arterial DSA what is the diagnostic accuracy of
  – contrast-enhanced MRA techniques
  – 3D TOF MRA techniques
  – 2D TOF MRA techniques
  – phase-contrast MRA techniques
  in determining stenosis of the internal carotid artery? In each case, measurements using the NASCET protocol only were included and the dichotomies used were:
  – 0–69% or 100% versus 70–99%
  – 0–49% or 100% versus 50–99%
  – 0–99% versus 100%.
- Compared with the gold standard of intra-arterial DSA, what is the diagnostic accuracy of the MRA techniques in identifying tandem lesions in carotid artery disease?
- What is the diagnostic impact of the MRA methodologies in comparison with duplex ultrasound?
- What are the long-term costs and outcomes of MRA and DSA in the diagnosis and management of people presenting with suspected carotid arterial disease.

Peripheral vascular disease

The research questions were:

- Compared with the gold standard of X-ray angiography what is the diagnostic accuracy of
  – contrast-enhanced MRA techniques
  – 3D TOF MRA techniques
  – 2D TOF MRA techniques
  – phase-contrast MRA techniques
  for identifying the severity of peripheral vascular disease? In each case the dichotomies used were:
  – 0–49% versus 50–100%
  – 0–49% or 100% versus 50–99%
  – 0–99% versus 100%.
  The question was addressed for all vessels, vessels above the knee and vessels below the knee.
- What are the long-term costs and outcomes of MRA and conventional angiography in the diagnosis and management of people presenting with peripheral vascular disease?

Chapter 3

Review methods

The chapter is divided into two parts. In the first, the literature review is described in terms of the search strategy, exclusion and inclusion criteria, assessment of relevance and validity, and data extraction. The second part is concerned with decision analytic modelling.

Literature review

To address the research questions presented in chapter 2, three separate searches were performed. The strategies are described here under the headings 'MRA', 'Outcomes' and 'Costs'.

MRA

The systematic search of the literature was conducted in two stages. In the first stage, electronic bibliographic databases and other electronic sources were searched.

The following electronic databases were searched using the search strategies given in appendix 1:

- MEDLINE
- EMBASE
- HealthSTAR
- Bath Information and Data Services (BIDS) –
  - Institute of Scientific Information
  - Science Citation Index
  - Index to Scientific and Technical Proceedings.

The search strategies were optimised for each search interface. The output of the searches was downloaded into a bibliographic database package (Reference Manager™, Research Information Systems) for further analysis.

All articles published from 1990 to the end of 1999 were included. To ensure all articles published in this period were available in the databases, the searches were repeated in March 2000 to allow for the delay of updating, particularly in MEDLINE. Significant overlap exists between the various databases. Two team members checked for duplication.

Three further electronic sources were searched.

- The Cochrane Library
- Inside, British Library
- Online Computer Library Centre.

For these sources less sophisticated searches were conducted (appendix 1) and the results were not immediately downloaded into Reference Manager. The results from these searches were first compared against the exclusion criteria and those references already in our Reference Manager database, so that only those articles likely to be of relevance and not already identified were included.

A complete Internet search was not performed, because our final inclusion criteria required published articles with sufficient data presented to complete a 2 × 2 table, so the searches of bibliographic databases were considered more appropriate. A limited Internet search was performed for reviews. We searched the sites of the Development and Evaluation Committee,[47–49] the South West R&D Directorate,[50] Health Evidence Bulletins – Wales,[51] the Canadian Coordinating Office for Health Technology Assessment,[52] the Swedish Council on Technology Assessment in Health Care,[53] Health Services Technology Assessment Text,[54] and New Zealand Health Technology Assessment Clearing House.[55]

In the second stage of the search, the lists of references in all relevant articles were handsearched to identify any additional relevant articles, and a list compiled of the journals in which the articles appeared. Journals that were not indexed in the electronic sources were identified. Details of relevant books were noted, but were not considered for inclusion in the review, as for this topic area it is unlikely that any high-quality primary research would be appear only in a book.

In our earlier reviews[2,41,56] we believed that our use of high-recall search strategies in a large number of resources, together with input from experts, meant that handsearching was not necessary. In this review we tested this hypothesis by handsearching a selection of key journals. Firstly, to include the journals that had potentially relevant articles, the ten most frequently occurring journals from a search of HealthSTAR using the MRA strategy (appendix 1) were selected. Secondly, to include journals that had contained articles

suitable for inclusion in the review, the ten most frequently occurring journals in the list of included articles (as at March 2000) were selected. The final list of ten key journals comprised the ten most frequently occurring journals in the combined list. The journals handsearched were *American Journal of Roentgenology*, *American Journal of Neuroradiology*, *Magnetic Resonance in Medicine*, *European Radiology*, *Investigative Radiology*, *Radiology*, *Journal of Vascular and Interventional Radiology*, *Journal of Vascular Surgery*, *European Journal of Vascular Surgery* and *Journal of Computer Assisted Tomography*. Handsearching was performed by two individuals and covered the years 1990 to 1999. Following training, the handsearchers applied exclusion criteria corresponding to the exclusion criteria that are described later.

Outcomes

To address the research questions presented in chapter 2 concerning the long-term costs and outcomes of MRA, it was necessary to seek evidence on the patient outcome following treatment allocation. Changes in patient outcome resulting from the use of MRA will depend both on any change in the treatment plan compared with that chosen using angiography and on the subsequent outcome of that treatment. No separate search was performed to identify such articles, as they were retrieved from the search described in the previous section. In order to identify relevant articles, all retrieved articles were checked for outcome data by two team members at the time when the final inclusion criteria were applied. A modelling approach was planned if there was insufficient evidence from trials in the literature. To provide data for the modelling approach, a separate search was used to identify studies that reported clinical outcomes of relevant interventions, whatever imaging method had been used. The interventions considered were drug or medical therapy, endarterectomy, reconstruction and percutaneous transluminal angioplasty. This search was conducted using the MEDLINE, EconLIT, Office of Health Economics Health Economic Evaluations Database and the NHS Economic Evaluation Database and the Cochrane Library. In the case of the Cochrane Library, only systematic reviews and meta-analyses were sought, and the search was limited to English-language articles. The search strategy is included in appendix 1.

Costs

To address the research questions about the long-term costs of MRA, additional evidence was required about the costs of evaluation and subsequent treatment and care. All retrieved articles in the main literature review of MRA were checked for resource use and cost data. It was anticipated that there would be insufficient cost information from the trials literature of MRA. Additional searches and reviews of published literature and national databases were conducted. Articles concerning the cost implications of MRA, angiography and other investigations associated with the conditions were identified from a search of the same databases used for the outcomes search, using the strategies shown in appendix 1. Department of Health databases (Hospital Episode Statistics, Health Related Resource Groups) were reviewed for data relevant to the resource use and/or costs associated with DSA, MRA, ultrasound and the management of carotid arterial disease or peripheral vascular disease.

Study selection

Diagnostic performance

Three sets of predefined exclusion and inclusion criteria were applied in sequence.

Electronic exclusion criteria

Full reports of original, patient-based studies were required. One of our later inclusion criteria was the need for there to be sufficient data reported for the construction of a 2 × 2 contingency table, and this is why letters and conference abstracts were excluded at this early stage. The following preliminary exclusion criteria were applied using the mechanisms available in each database (except the Index of Scientific and Technical Proceedings):

- review articles
- editorials
- letters
- case reports
- conference abstracts
- non-human studies (these include animal, *in vitro*, phantom and *post mortem* studies).

Secondary exclusion criteria

More specific criteria for exclusion were applied to the abstracts of articles and the preliminary exclusion criteria were re-checked by at least one reviewer. The exclusion criteria were applied in the order shown below, so that only the first applicable criterion was noted. In many cases more than one criterion would have been relevant. The criteria were:

- not MRA
- not carotid or peripheral arteries
- study of technical performance

- study with paediatric subjects
- ten or fewer patients in the study group.

If no abstract was available or if insufficient information was given in the abstract, the full article was retrieved and the exclusion criteria applied.

Final inclusion criteria

Full copies of all remaining articles were obtained. All the exclusion criteria were reapplied to the full article. Two reviewers applied the following final inclusion criteria for the two clinical applications considered.

Carotid artery stenosis:

A. A study comparing MRA with digital subtraction angiography or cut-film angiography.
B. Sufficient data reported for the construction of a 2 × 2 contingency table.
C. Performance at 50%, 70% or 100% stenosis reported (see chapter 1).
D. Not a duplicate study of the same patient group. Where more than one study was found, the one using the largest patient group was included.
E. All patients in the study received selective carotid intra-arterial digital subtraction or cut-film angiography.
F. The method used to determine the degree of stenosis was described.
G. No asymptomatic patients were included.
H. No time delays of over 1 month occurred between examinations.

Peripheral vascular disease:

A. A study comparing MRA with digital subtraction angiography or cut-film angiography.
B. Sufficient data reported for the construction of a 2 × 2 contingency table.
C. Clearly specified that all patients were symptomatic.
D. Conventional angiographic technique described.
E. Time delay between examinations was under 1 month.
F. Not a duplicate study of the same patient group. Where more than one study was found, the one using the largest patient group was included.

These criteria were chosen following extensive discussion by the review panel. In both cases, criteria A and B are necessary to ensure a robust investigation of diagnostic performance. For carotid artery disease, criterion C ensures that the data have relevance to surgical decision thresholds (see chapter 1). The requirement for the patients to be symptomatic is intended to minimise bias in the results caused by differences in patient characteristics within the cohort. Conditions about time delays minimised differences in results caused by disease progression. Duplicate studies on the same patient group were excluded to prevent that patient group being included twice and possibly influencing the results. These issues of study validity are considered further in the section on data extraction.

Non-English-language literature

Non-English-language literature was not excluded on the basis of language. Where an English abstract was available, the preliminary electronic and secondary exclusion criteria were applied to the English abstract. Otherwise, the full article was obtained and the two sets of criteria were applied without full translation of the article. Where the article was written in French, German or Spanish it was not translated, and the final inclusion criteria and data extraction were performed with the help of a dictionary. People having the relevant language as their first language were recruited to help apply the final exclusion criteria where the paper was in Japanese, Russian, Polish or Italian. A reviewer, together with a native speaker where necessary, then performed data extraction.

Outcomes and costs

The preliminary electronic and secondary exclusion criteria described for diagnostic performance papers were applied. Remaining articles were excluded if they did not include a health economics analysis or details of patient outcomes that could be included in the decision analytic models.

The studies were assessed to determine: the source of resource use and cost data; methods used to value resource use and patient benefits; methods of analysis and generalisability of results. The studies were classified into the following categories:

- prospective resource use and patient outcome data
- mixed prospective and retrospective data
- retrospective data.

These categories were further subdivided as follows:

- randomised controlled trial
- controlled trial (pseudo-randomisation or no randomisation)

- cohort study with concurrent controls
- cohort study with historical controls.

Prospective data were preferred to retrospective data and randomised controlled trial data preferred to non-randomised data. Studies using expert opinion to derive estimates of the cost or value resource use or patient outcome were excluded. Cost data that did not report resource use and costs separately, used charge data or did not report resource use or costs that were generalisable to the UK setting were excluded.[57–59] Studies that included valuations of health outcomes based on time trade-off or standard gamble techniques were preferred to those based on preferences or visual analogue scales.[58,59]

Data extraction and assessment of validity

Diagnostic performance

Checklists were designed to cover study design, patient characteristics, technical details and potential biases in study execution (appendix 3). One reviewer and one clinician or radiographer team member completed the checklists for each article. Consensus was reached on any disagreements.

Studies were grouped by the MRA technology used, and results of studies were extracted and summarised by one team member. For articles on carotid artery stenosis, data were extracted for three diagnostic thresholds: 0–69% or 100% versus 70–99%; 0–49% or 100% versus 50–99%; and 0–99% versus 100%. These thresholds were chosen to correspond with the decision thresholds used in the NASCET[8] and ECST[9] trials on carotid endarterectomy, as explained in chapter 1.

For articles on peripheral vascular disease, data were extracted for three diagnostic thresholds, the first of which differs from that used for carotid artery stenosis: 0–49% versus 50–100%; 0–49% or 100% versus 50–99%; and 0–99% versus 100%. These thresholds were chosen as they represent clearly defined anatomical differences with regard to the severity of disease.

The results of each primary diagnostic performance article were expressed using the following summary statistics: sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratios. The prevalence was also determined for the subject group under investigation. The expressions used to calculate these statistics are given in appendix 5.

Summaries were written for each article and tables completed, describing the aims and methodology of the study, emphasising possible causes of bias in the results[60–62] and reasons for comparability, or otherwise, with other articles. The authors' conclusions were also summarised.

Some of the threats to study validity were minimised by the choice of the inclusion criteria. For both carotid artery stenosis and peripheral vascular disease it was necessary for comparison to be made with a defined gold standard investigation (i.e. conventional angiography). For the carotid artery stenosis articles, criterion E corresponds with the risk of verification bias; other potential biases arising from imperfect use of the gold standard were noted on the bias checklist. For both disease groups the risk of patient cohort biases was minimised by specifying that the patient groups must include only symptomatic patients. The possibility of disease progression bias in included articles was minimised by specifying a time delay between MRA and conventional angiography of under 1 month. Other biases generally considered to pose the greatest threat to study validity[63,64] are those related to the patient cohort and independence of interpretation. The comprehensive bias checklist (appendix 3) covered these, and their effect was investigated using multiple linear regression analysis, as described in the section on data synthesis.

Costs

Data were extracted and summarised by two team members.

Data synthesis

Diagnostic performance

The sensitivity and specificity results from the independent studies were grouped by MRA technique and the diagnostic threshold used, as described in the previous section. Results from the independent studies were plotted on sensitivity versus 1 – specificity axes, which can aid the visualisation of the scatter of results. Where more than one set of results were presented from a single patient group, only one set was included. If more than one observer was used, the results of the first were included. If more than one method within the same MRA technique was used, the better set of results was included.

Where five or more sets of results were available using the same MRA technique and diagnostic threshold, the results from the independent studies were combined in a meta-analysis using a summary receiver operating characteristic (SROC) curve,[65–68] as recommended by the Cochrane Screening and Diagnostic Tests Methods Working Group.[69] The assumption behind this method is that the results from different studies can be represented by a single receiver operating characteristic (ROC) curve. It is easier mathematically to fit a straight line to a set of points than to fit a curve, so the sensitivity and specificity data were transformed using a logistic function so that a linear relationship would be expected between them. To prevent undefined values on logistic transformation, a contingency adjustment[5] of 0.01 was applied to all true-positive, false-negative, true-negative and false-positive values if any one was zero. A straight line was fitted to the transformed results using an unweighted least-squares fit, an inverse transform was performed on the fitted line, and the result plotted as a SROC curve. SROC curves are increasingly common in radiology,[70–73] although it is important to realise that the assumption of an underlying curve does not explain all the heterogeneity between results.[74] This curve is itself a summary, but for comparison purposes a further statistic Q^* and its 95% confidence interval (CI)[65] were calculated. Q^*, also known as the maximal joint sensitivity and specificity, is the point on the SROC curve where sensitivity and specificity have the same value. Q^* is a sensible summary value when there is no particular advantage to maximising sensitivity or specificity at the expense of the other. This is the case here, where patients with false-positive results needlessly undergo the risks of surgery, but those with false-negative results are denied its benefits. Q^* would not be a good choice for describing a screening test, where one aims to have no false-negative results at all, but can accept a few false-positive ones.

In the case of carotid artery stenosis, articles were grouped by the MRA technique used in assessing the extracranial portion of the internal carotid artery. For peripheral vascular disease, articles were first grouped by MRA technique without regard to the anatomical location of the vessels studied. Where possible, a further subdivision was made within the technique groups into results from above and below the knee.

Where four or fewer sets of numerical results were available, SROC analysis was not performed at all and results were synthesised by qualitative descriptions or using the decision analytic model.

The effect of study design features and other factors on the fit of the linear model was assessed using a multiple linear regression analysis.[75] In each case a 95% significance level was chosen, the p value used to determine significance being dependent on the number of variables assessed in the multiple linear regression analysis. Where n variables were assessed, the requirement was for p to be less than $0.05/n$.[76]

For carotid artery stenosis articles, all articles reporting results for the 0–69% or 100% versus 70–99% threshold were included in the multiple linear regression analysis. The five variables chosen for investigation by regression analysis were:

- MRA technique
- inclusion of asymptomatic patients
- the risk of test or diagnostic review bias
- the risk of verification bias
- the risk of withdrawal bias.

It has been implicit in the method chosen for data synthesis up to this point that the diagnostic performance was expected to be different for the various MRA techniques. The linear regression analysis was designed to determine if differences were statistically significant. The presence of asymptomatic patients in the patient group is an indicator of possible patient cohort bias, while the last three categories represent the biases that pose the greatest threat to the validity of the results.[63] An article was classified as being free of the risk of each bias only if information was explicitly given in the article.

Although the effect of other study features noted in the checklists was of interest, because of the relatively small number of studies in the analysis it was decided not to include further variables in the regression analysis. Instead, as part of the consideration of possible reasons for heterogeneity between studies, a univariate linear regression analysis was performed only if a qualitative observation was made at this stage about a possible influence on the results. This was done only once (for the 2D TOF carotid artery stenosis results at the 0–69% or 100% versus 70–99% diagnostic threshold). An investigation was made of the effect of the year of publication on the published results, as the earlier results appeared to be less good. Articles were classified as being published in 1994 or before versus 1995 onwards.

For peripheral vascular disease articles all studies reporting results for the 0–49% versus 50–100% threshold were included in a regression analysis. The five variables chosen for investigation were

- MRA technique
- inclusion of normal segments
- the risk of test or diagnostic review bias
- the risk of verification bias
- the risk of withdrawal bias.

The inclusion of normal segments has great potential to cause differences in diagnostic performance between articles, and represents a risk of patient cohort bias.

To determine if different results were obtained above and below the knee, a univariate analysis was performed on the subset of studies that reported results separately for the two regions, for the 0–49% versus 50–100% threshold.

The same approach to the analysis of study features that might cause heterogeneity was taken as for the carotid artery stenosis analysis. In the case of peripheral vascular disease, however, no further univariate analyses were performed.

To detect publication bias, funnel plots were constructed.[61,77] The size of each study was plotted as a function of the natural logarithm of the diagnostic odds ratio. For the carotid artery stenosis studies, the study size was expressed in terms of the number of vessels investigated in the study. For the peripheral vascular disease studies, the study size was expressed in terms of the number of patient segments investigated. The diagnostic odds ratio is a measure of the ability of the test to discriminate positive from negative cases, and is defined in appendix 5. A symmetrical, funnel-shaped distribution of points indicates the absence of publication bias. An asymmetrical or skewed distribution, especially the absence of small studies with a low diagnostic odds ratio, suggests the presence of publication bias. The symmetry of the funnel plots was assessed informally by visual inspection.

For carotid artery stenosis, qualitative synthesis was performed to draw together the results on the identification of tandem lesions and comparisons with duplex ultrasonography.

Outcomes and costs

Preliminary assessments of the literature indicated that the published trials of MRA did not include economic evaluations of the costs and outcomes of the diagnostic evaluations, short-term management strategies or longer term care. In this situation, formal quantitative methods to synthesise the reported outcomes and costs of MRA were not appropriate and not planned. The methods used to derive estimates of the costs and outcomes for the decision analytic models are described in the next section.

Decision analytic modelling

The primary objective of modelling was to identify the relative cost-effectiveness of MRA when compared with the gold standard of X-ray angiography.

Perspective

Ideally, cost-effectiveness analyses should take a broad societal perspective, to include the health outcomes and costs of everyone affected by the intervention. This analysis uses the perspective of the funders or providers of healthcare and social care, and patients, which are the key components of a societal perspective. Within this, the analysis will identify the relative cost-effectiveness of MRA from specific perspectives:

- For purchasers of MRA equipment a key question is: What is the cost-effectiveness if MR were purchased solely for the diagnosis and management of carotid artery disease, or solely for peripheral vascular disease?
- For the physician a key question concerns the optimal assessment strategy for patients presenting with carotid artery disease.
- For the vascular surgeon a key question concerns the optimal assessment strategy to detect stenoses, occlusion, satisfactory inflow vessels and patent distant vessels to aid decision-making in peripheral vascular disease.

Comparators

The analysis assessed the relative cost-effectiveness of MRA compared with alternative tests, in particular with X-ray angiography and DSA. The relative benefits of the tests are outlined in chapter 1. The economic analysis investigated the consequences of the trade-off between accuracy (measured in terms of sensitivity and specificity) and resources used in terms of health outcomes and costs. The alternative of duplex ultrasound is considered in this analysis when it is used in combination with MRA in the case of carotid artery disease. Two separate decision trees were developed, one for carotid artery disease and one for peripheral vascular disease. These allowed a

cost-effectiveness analysis of the costs and outcomes of different diagnostic interventions.

Decision trees

Carotid artery disease

Figure 5a illustrates the structure of the carotid artery stenosis decision tree. The analysis assessed the costs and outcomes of surgery or medical management for 10 years from the initial evaluation with MRA or DSA. The risk of stroke and death from all causes was included for 5 years from surgery or initiation of medical management. The risk of stroke or death after 5 years is relatively low. Clinical trial data indicate that the annual risk differences between endarterectomy and medical management also decline after this time. For the purpose of this analysis it was assumed that that there would be no differences in the risk of stroke or death between endarterectomy and medical management after 5 years.[8,9]

The tree starts with patients who have experienced transient ischaemic attack or minor stroke and who require diagnostic evaluation to detect the degree of stenosis. The purpose of the diagnostic evaluation at this point is to explore whether the degree of stenosis is less than 70% or occluded, or if it is between 70% and 99%. The degree of stenosis will determine if the patient is suitable for surgical procedures (endarterectomy) or medical management. It is assumed that the patient has already been assessed for other risk factors that will affect the management decision. At this point there is a choice between the three tests included in the analysis:

- X-ray angiography (DSA)
- MRA
- duplex ultrasound plus MRA.

DSA was defined here as the gold standard test, which is used to evaluate the comparative effectiveness of other methods of diagnosis and evaluation. For this reason, the sensitivity and specificity of DSA were, in this analysis, set equal to 100%. This may seem to imply that there is no risk of false-positive (individuals for whom the test is positive but they do not have the disease) or false-negative (individuals for whom the test is negative but they do have the disease) results using DSA. In fact it is just a consequence of using the test as the comparator. DSA is an invasive test. The first chance node (following DSA) reflects the risk of stroke or death as a consequence of the test itself. Patients who have stroke following DSA will survive with no disability, minor or major disability, or die. If DSA does not cause stroke or death the patient may undergo endarterectomy or receive medical management, depending on the result of the test.

According to clinical guidelines,[8,9] patients with a severe carotid stenosis (≥ 70%) should undergo carotid endarterectomy, while patients with only a mild (< 30%) or moderate (30–69%) stenosis should not be subjected to surgery. If patients have a degree of stenosis lower than 70% or occlusion, they should receive medical management. If endarterectomy is not performed, medical management is not the only alternative. For example, percutaneous transluminal angioplasty is a procedure that has been advocated for patients suffering from carotid artery stenosis.[78] In the UK, however, 99% of patients (expert opinion) undergo endarterectomy or receive medical management. Detailed information was not available about the relative use of medical management or other alternatives for those patients who were not eligible for endarterectomy. In particular, it was not possible to calculate the appropriate use of alternative management strategies by the degree of stenosis of the patient. Thus the analysis was focused only on these two alternatives.

The events following initiation of medical management for patients with stenosis less than 70% (*Figure 5b*) reflect the risk of transient ischaemic attack or stroke within 32 days and the subsequent 5 years. (The 32-day period is based on the immediate follow-up in the NASCET and ECST trials.) The following chance node reflects the patients' risk of having a transient ischaemic attack or stroke within 1 year from the first episode (minor stroke or transient ischaemic attack at the beginning of the tree). Finally, four health states have been identified: alive and well, alive with non-disabling stroke (modified Rankin score < 3), alive with disabling stroke (modified Rankin score 3–5) and dead. The probability of ending in one of these states is determined by previous events.

For patients with a stenosis higher than 70% undergoing carotid endarterectomy there is a risk of perioperative complications (ischaemic and haemorrhagic stroke, myocardial infarction, local complications). These are synthesised in *Figure 5c*. In the case of stroke, patients may survive or die. If they survive they may experience a transient ischaemic attack or stroke within 5 years. As before, they will progress to one of the four health states previously described. If patients do not have perioperative complications they may have a transient ischaemic attack, stroke, no transient ischaemic attack or no stroke, and the subsequent health consequences.

The structure of the tree is identical for the other diagnostic and evaluation strategies. However, the probability of events varies between the alternative methods. In particular, the diagnostic accuracy of the alternatives to DSA may be less than 100%. If the diagnostic evaluations are associated with a probability of false-negative results, then there will be a higher risk (compared to DSA) of transient ischaemic attack and stroke and subsequent poor health outcomes. If the diagnostic evaluations are associated with a probability of false-positive results, then a higher proportion of patients will undergo unnecessary carotid endarterectomy (compared to DSA) and be exposed to the risk of perioperative complications.

Peripheral vascular disease

The decision tree for the peripheral vascular disease model is illustrated in *Figure 6*. The analysis assessed the risks, costs and outcomes (using descriptions of mobility) of surgery, percutaneous transluminal angioplasty or medical management for 1 year from the initial evaluation with MRA or DSA. The evidence about the relative long-term benefits (in terms of mobility and health status) of alternative treatment strategies for peripheral vascular disease is limited and uncertain.[79–81] It was felt that use of a time frame longer than 1 year for the analysis, with a high level of uncertainty about these outcomes of treatment, would mask the costs, outcomes and uncertainty resulting from the use of the alternative diagnostic techniques.

Two alternative tests are considered in the model: preoperative MRA followed by intraoperative arteriography or preoperative DSA followed by intraoperative arteriography. Intraoperative arteriography is not often used in practice, but has been included in the model to allow decisions about the correctness of the diagnosis to be incorporated. The tree starts with a patient with peripheral vascular disease who is thought to have critical limb ischaemia (gangrene or ulceration, with or without rest pain) or severe claudication that requires surgery or percutaneous transluminal angioplasty. The decision concerns the choice of diagnostic evaluation to plan limb salvage procedures (bypass surgery, percutaneous transluminal angioplasty) or amputation. Key information from the diagnostic evaluation includes the identification of occlusions, degree of stenoses, length of stenoses or occlusions and availability of patent vessels for bypass surgery.

At surgery it might be confirmed that the diagnostic evaluation has correctly identified the degree of stenosis, the length of stenoses or occlusions and availability of patent vessels, and a correct treatment plan that is followed. Alternatively, the plan may be inaccurate.

In the model shown in *Figure 6*, the allowed treatment plans are:

- medical management for patients with stenoses of less than 50%
- percutaneous transluminal angioplasty for stenoses of 50–100% and 10 cm or less in length
- bypass surgery for stenoses of 50–100% and greater than 10 cm in length, provided that patent vessels are available for the graft
- amputation for stenoses of 50–100% and greater than 10 cm in length, if there are no suitable distal vessels.

These plans have been somewhat simplified to facilitate modelling. For example, percutaneous transluminal angioplasty is sometimes performed for stenoses over 10 cm in length or medical therapy may be used in the fourth group before resorting to amputation.

If the surgical plan is correct and followed, then there is a chance of complications (e.g. graft failure, amputation, death) or no complications. Each of these will result in the patient ending in one of six health states: fully ambulant, limited ambulance and independent, limited ambulance and dependent, non-ambulant using a wheelchair, bedridden or dead.

If the surgical plan is incorrect at the time of surgery, the surgeon may carry out the planned procedure with modifications or change the type of procedure. For example, if a bypass procedure was planned this may be changed to percutaneous transluminal angioplasty or amputation. Again there may be complications or no complications from the procedure and the patient ends in one of the six health states.

For the peripheral tree, the risk of stroke or death as a consequence of DSA is not included, since the design of the tree is such that all patients have intraoperative arteriography. As with the tree for carotid artery disease, DSA is defined as the gold standard test (i.e. sensitivity and specificity of 100%) to determine the degree of stenosis or occlusion of visualised vessels. However, DSA may not accurately determine the length or severity of lesions, or the availability of patent vessels for bypass surgery,[82,83] leading to the formulation of an inaccurate treatment plan.

Variable estimation

Probabilities of events

The probabilities that an evaluation accurately identified the degree of stenosis were estimated as the average (mean) rate and standard deviation from the evidence collected for this systematic review. These were weighted by the patient sample size of the trials. The probabilities of subsequent events related to diagnosis and treatment were estimated from the outcomes literature review as the best estimate (range).

For the carotid artery disease model, the probability of undergoing endarterectomy was set equal to the probability that the test result is positive (70–99%), and the probability of medical management was set equal to the probability of a negative result (0–69% or 100%). For the peripheral vascular disease model, the probability that the treatment plan is for surgery or percutaneous transluminal angioplasty was set equal to the probability that the test result is positive for visualised vessel segments (50–100% stenosis). The probability of medical management was set equal to the probability of a negative result (0–49% stenosis). The probability that the treatment plan for surgery is correct was set equal to the probability that there is concordance between the treatment plan and intraoperative findings.

Costs of events

The costs of healthcare resources used as inputs to the diagnostic evaluations, surgical and medical management, and follow-up and treatment of complications were included. The costs were estimated as the product of resource use and unit costs for each diagnostic evaluation and subsequent events, as determined from the literature. For each cost item, data on resource use and unit costs were extracted from the reviewed literature and databases. Where more than one estimate for each cost item was obtained, the range of values found was used to generate a triangular (if there were more than two estimates) or uniform (if there were only two estimates) distribution for the simulation analysis. The distribution for each variable included the minimum, mean or median and maximum values found. If it was possible to derive a mean value and measure of variance (e.g. standard deviation or 95% CI), this information was included. The costs of the diagnostic evaluations were derived from local activity data. These were supplemented by estimates from the national databases. The national databases were used to provide minimum and maximum estimates for the distributions used in the simulation analysis. The costs of diagnostic equipment for DSA and MRA were estimated as the list purchase costs of the equipment, annuitised over the expected life of the equipment. The annual cost of equipment was then divided by the number of minutes per year it could be utilised. For the base case analysis it was assumed that the equipment utilisation rate was 100%. The minutes per year of utilisation was estimated as the number of sessions per day multiplied by the number of minutes per session, multiplied by the number of weeks for which the equipment could be used. Implications of these assumptions are discussed in chapter 8.

Final outcomes

Utility values for the health states were assigned as the end-points of the decision trees. These were used to estimate expected QALYs. The states of no disability and death were used as anchor states, with values of 1 and 0, respectively. The QALYs were estimated as the product of utility values and estimated life expectancy.

Expected costs and outcomes

The expected costs of the model were estimated as the sum of the costs of events leading to each end node in the decision tree, multiplied by the probability of reaching that end-point. The expected outcomes were estimated as the sum of the outcomes associated with each end node in the decision tree multiplied by the probability of reaching that end-point.

Discounting

The long-term costs and outcomes associated with the final health states of the model were adjusted to net present values. The choice of discount rate is uncertain and subject to debate.[58] The analysis will use the discount rates specified by the UK Treasury[84,85] for the base case analysis (6% for costs, 1.5% for outcomes). The impact of this on the expected QALYs and incremental cost-effectiveness ratios was tested in a sensitivity analysis by increasing the discount rate for outcomes to 6%. The objective of the economic analysis was to provide information relevant to the UK NHS. The discount rates used in alternative jurisdictions (e.g. the USA) were not felt to be applicable.

Model uncertainty: sensitivity analyses

Two approaches were used to deal with uncertainty in the model. The first was to use simulation to generate mean expected costs and outcomes and statistical measures of expected variance around the mean and standard deviation (probabilistic sensitivity analysis). This was used for variables where there were sufficient data to estimate a

mean value and distribution, or where a plausible range of values could be estimated.

To explore the uncertainty associated with the structure of the model, methods of analysis, or variables for which mean values could not be estimated, one-way sensitivity analyses were performed. The following parameters were of particular interest for the sensitivity analysis:

- The sensitivity and specificity of MRA. For the base case these were estimated as mean values from the systematic review, using simulation to give a measure of the uncertainty arising from variance around the mean value. However, this will exclude two important sources of additional uncertainty. The first is the impact of the inclusion and exclusion criteria for the systematic literature review. The second is that the sensitivity and specificity of diagnostic evaluations may be linked, so that improvements in one value are at the expense of reductions in the other. In this case it is not clear where the optimal balance between sensitivity and specificity lies. This would not be captured by the simple simulation analyses. Additional simulations were therefore conducted, using pairs of sensitivity and specificity values predicted from the clinical trial data.
- For the carotid case, the probability of stroke or transient ischaemic attack following medical management or endarterectomy.
- The discount rate.
- The time frame of the analysis.

Analysis of data

The primary and sensitivity analyses were each conducted in two stages. First, a comparison of the mean and standard deviation of expected costs and outcomes was made. If both the expected costs and outcomes of the alternative diagnostic interventions were equivalent, then incremental cost-effectiveness ratios for that analysis were not calculated. Similarly, if one diagnostic evaluation was associated with both higher costs and lower outcomes, then this was said to be dominated and was excluded from further analyses.[43,58] Where further analysis was performed, the remaining diagnostic evaluation strategies were compared to the least-cost method, using incremental cost-effectiveness ratios. Incremental cost-effectiveness ratios were calculated as:

$$\frac{\text{expected cost of A} - \text{expected cost of B}}{\text{expected outcome A} - \text{expected outcome B}}$$

Statistical measures of variance around the incremental cost-effectiveness ratios were not calculated, and no predefined target norm for cost-effectiveness was chosen.

Data

The probability data were estimated from the systematic review of the diagnostic evaluations described in the first part of this chapter. These were supplemented by the 'outcomes' literature review for the probabilities of events that were subsequent to complications of DSA and the surgical procedures included in the model.

The resource use and costs and health state utilities were estimated from the 'costs' literature review, information from Leeds Teaching Hospitals NHS Trust, from the York District Hospital and from the Central Manchester Healthcare Trust. Missing data for these variables were estimated based on expert opinion in vascular surgery, radiology and neurology from the review team members.

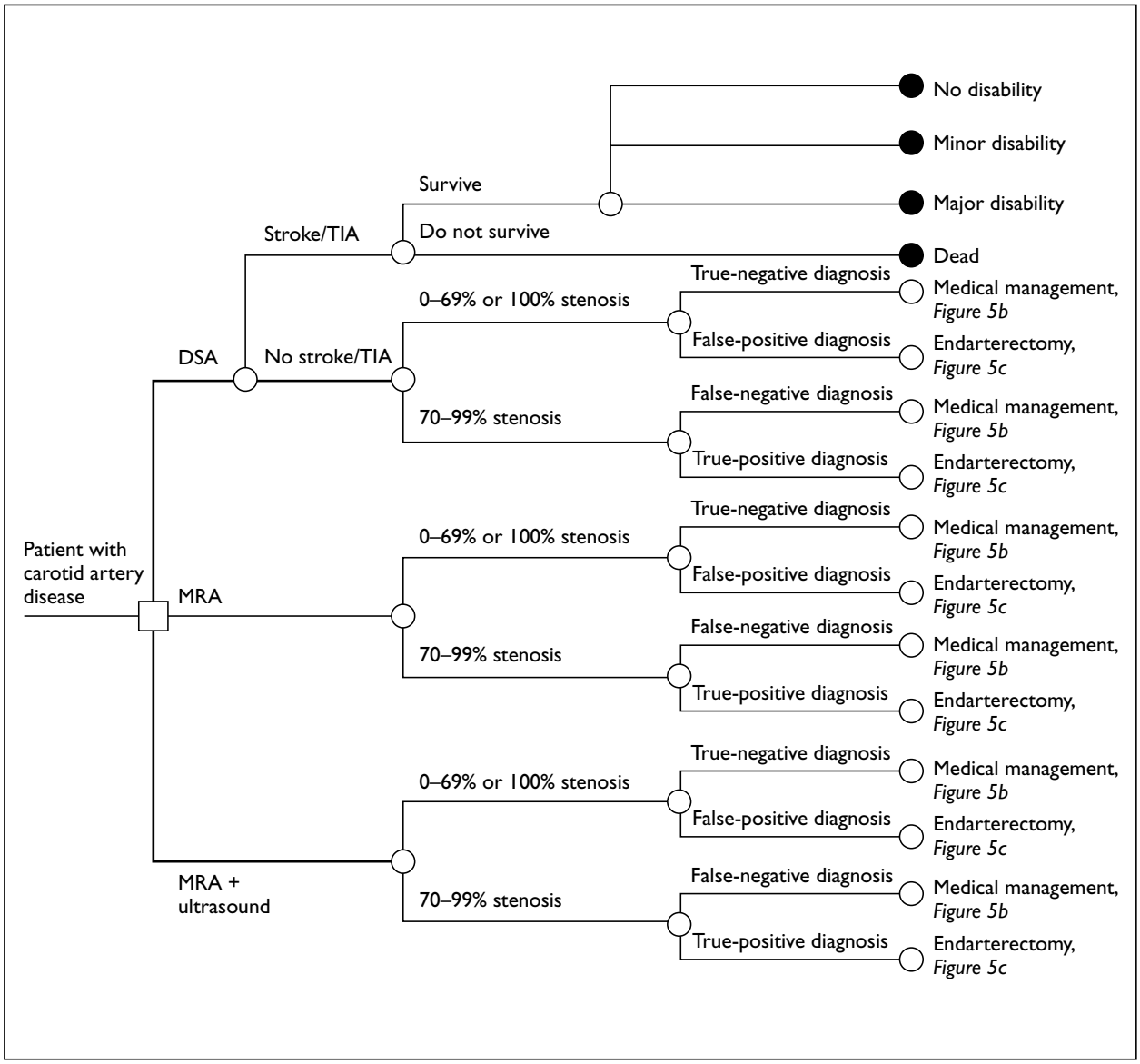

FIGURE 5a *Carotid artery stenosis decision tree: initial diagnosis. TIA, transient ischaemic attack (□, Decision node; ○, chance node; ●, final outcome)*

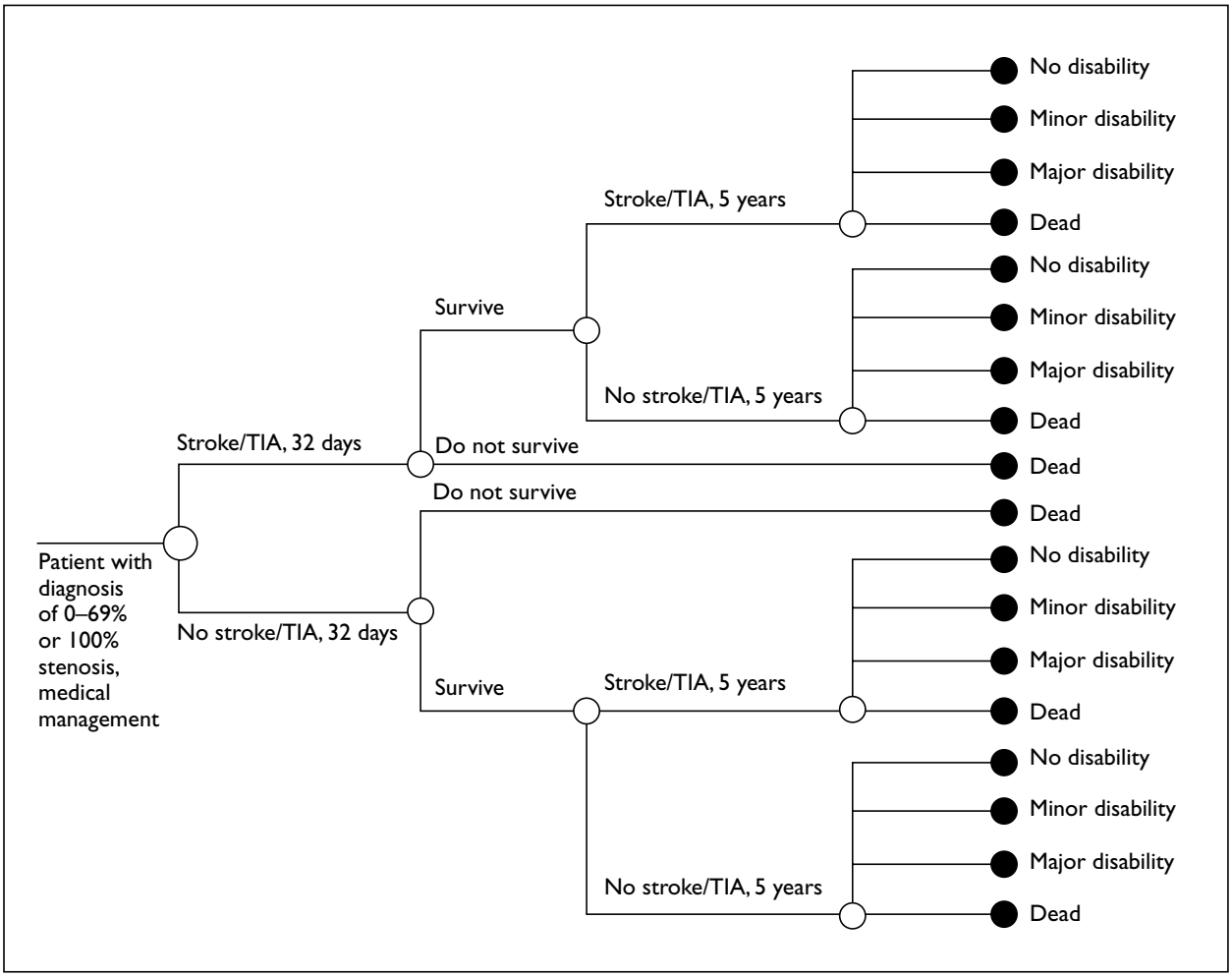

FIGURE 5b *Carotid artery stenosis decision tree: negative diagnosis of 0–69% or 100% stenosis, leading to medical management (○, Chance node; ●, final outcome)*

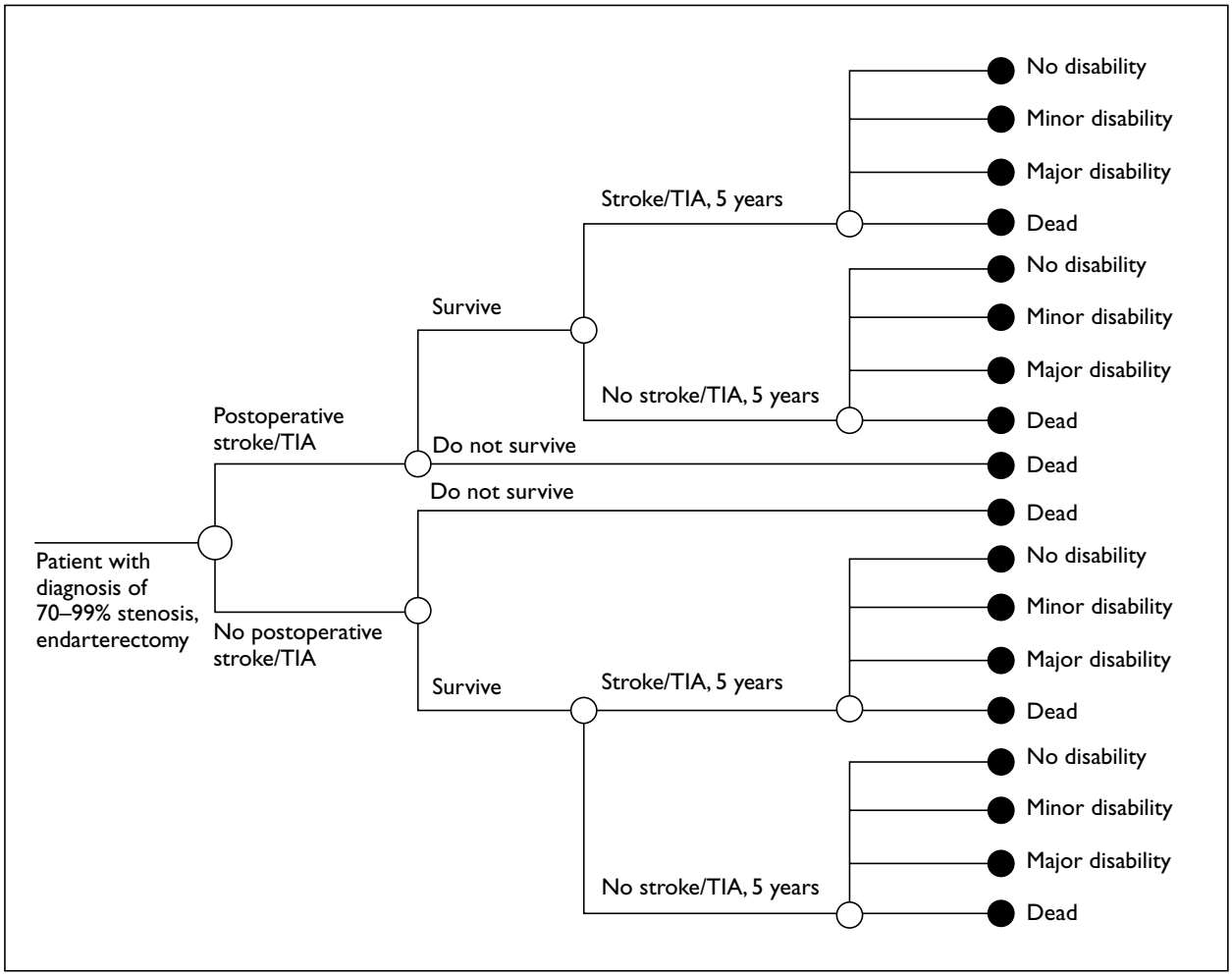

FIGURE 5c *Carotid artery stenosis decision tree: positive diagnosis of 70–99% stenosis, leading to endarterectomy (○, Chance node; ●, final outcome)*

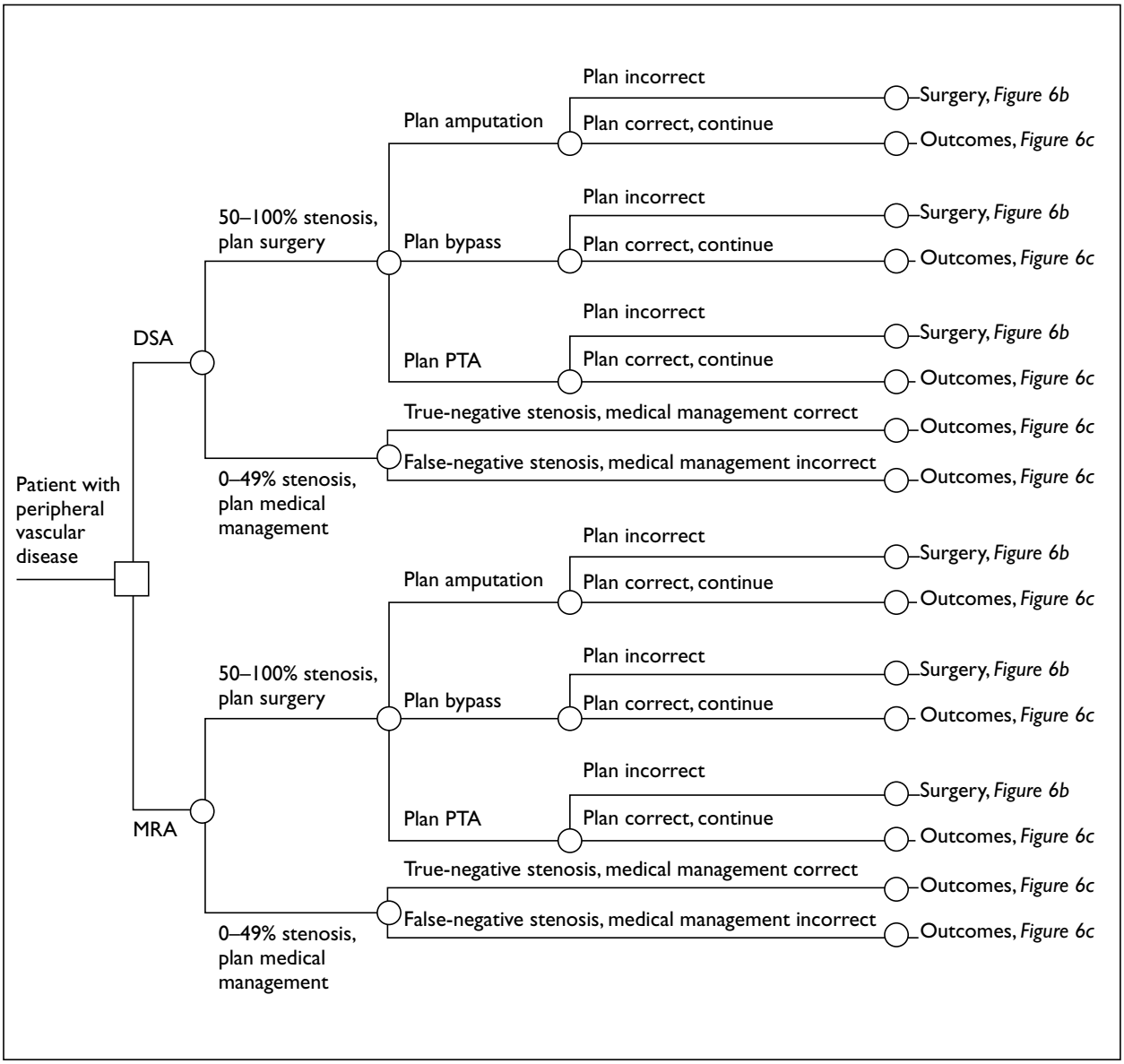

FIGURE 6a *Peripheral vascular disease decision tree: initial diagnosis. PTA, percutaneous transluminal angioplasty (□, Decision node; ○, chance node)*

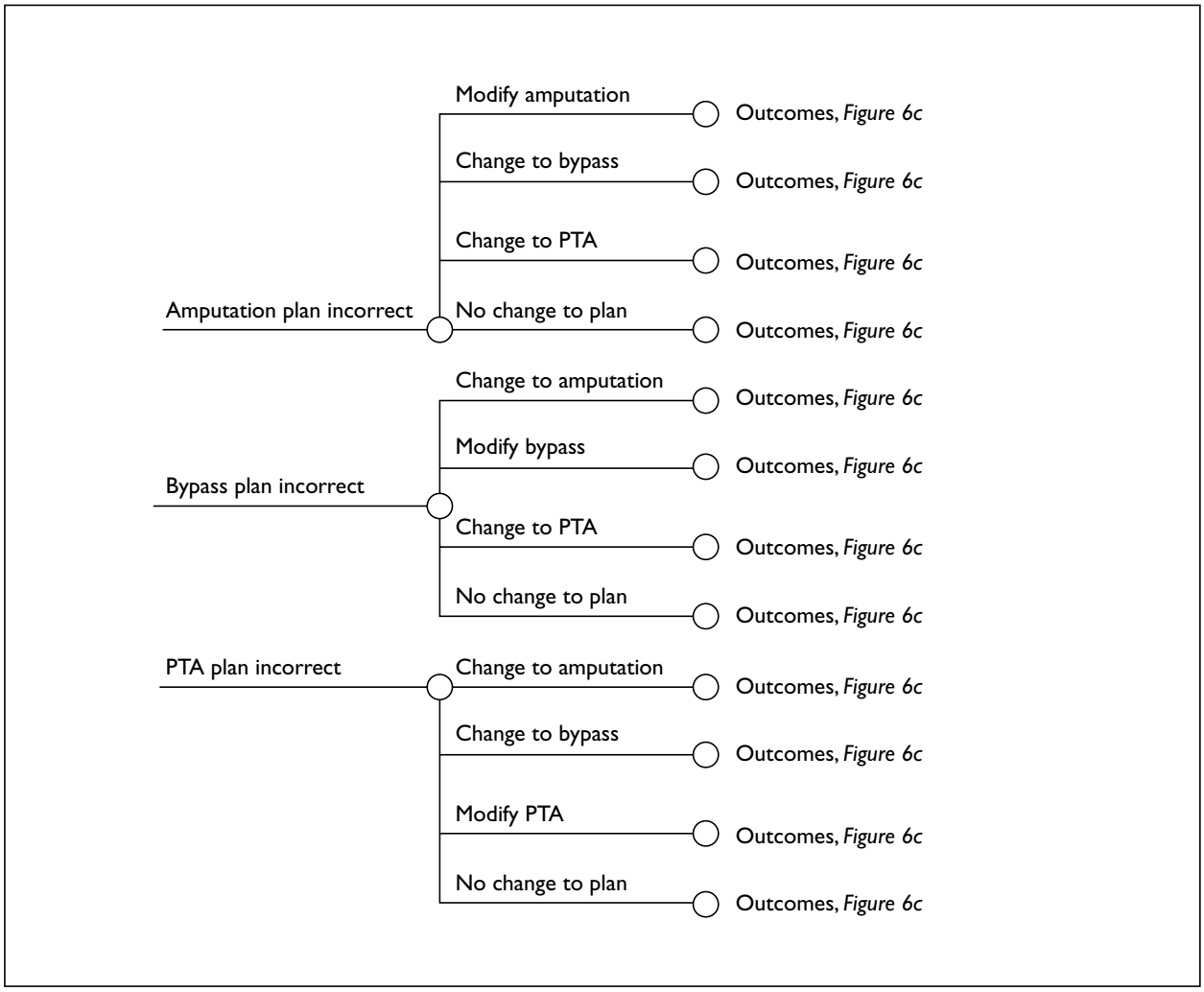

FIGURE 6b *Peripheral vascular disease decision tree: outcomes of incorrect surgical plan (○, Chance node)*

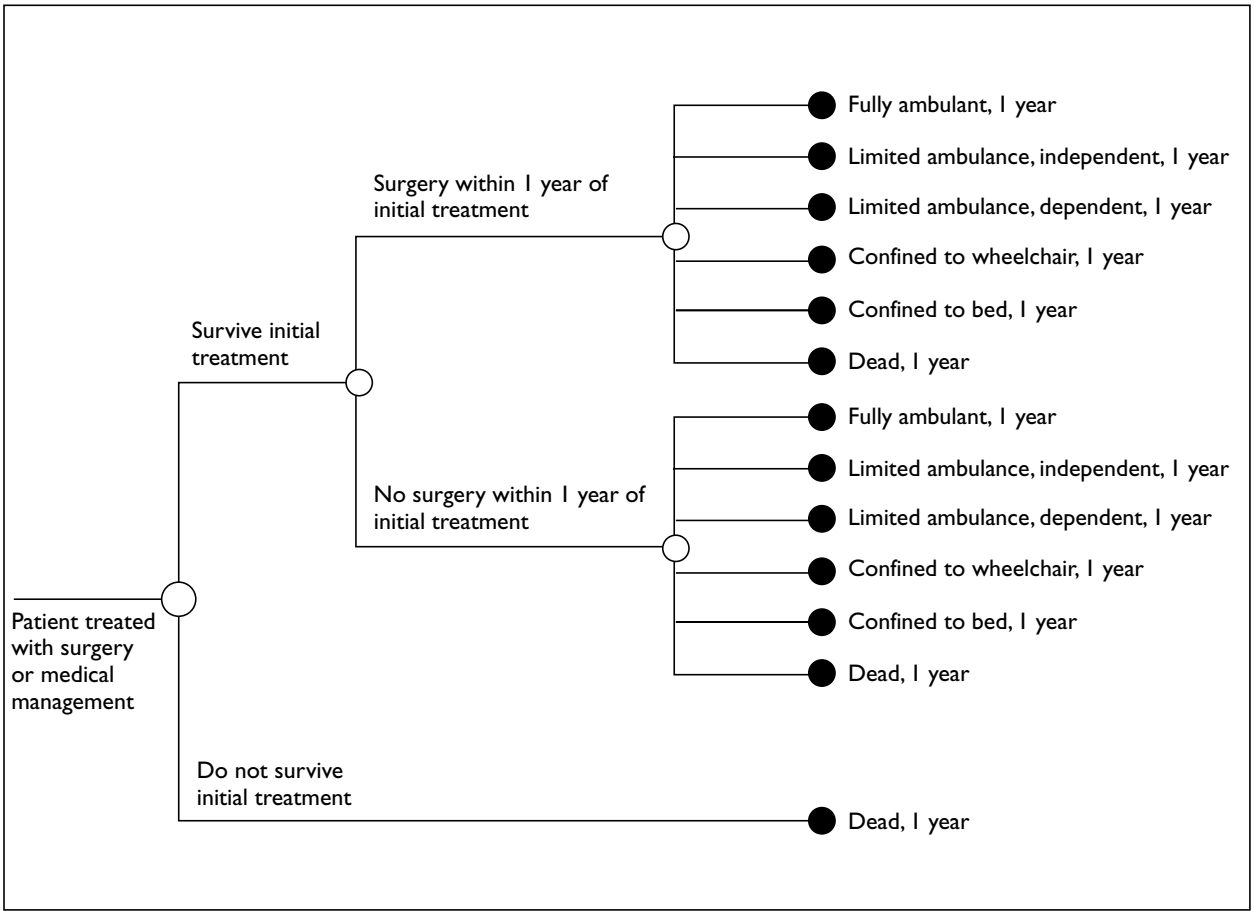

FIGURE 6c *Peripheral vascular disease decision tree: outcomes of correct surgical plan (○, Chance node; ●, final outcome)*

Chapter 4

Details of studies included in the review

This chapter is divided into three sections. In the first, for those with an interest in methodological issues associated with systematic literature reviews, detailed information is given about the numbers of articles considered and excluded at each stage of the search process. This is followed by descriptions of the articles included in the review, separately for carotid artery stenosis and peripheral vascular disease.

Detailed analysis of search methodology

MRA

The results of searching the main electronic bibliographic databases and the numbers remaining after exclusion of duplicates are shown in *Table 1*. The results of applying the preliminary electronic exclusion criteria using the facilities provided by the electronic bibliographic databases are given in *Table 2*. The results of applying the secondary exclusion criteria are given in *Table 3* (exclusions) and *Table 4* (inclusions). The results of applying the final inclusion criteria are given in *Tables 5* to *8*. One article[86] that could not be eliminated using the preliminary and secondary exclusion criteria was missing from the British Library collection and we were unable to obtain a copy elsewhere.

BOX 1 The 24 journals identified from Inside and the Online Computer Library Centre that are not indexed or are only partially indexed elsewhere

Advances in Vascular Surgery
Applied Radiology
Arztliche Praxis
Brain and Nerve
Cardiovascular Research
Der Radiologe
*Diagnostic Imaging**
Electromedica
Emergency Medicine
Japanese Journal of Nephrology
Journal Nihon University Medical Association
Journal of Stroke and Cerebrovascular Diseases
*Kardiologgiia**
La Revue du Practicien
*Lecture Notes in Computer Science**
*Medicamundi**
Modern Medicine
Nihon Igaku Hoshaen Gakki Zasshi
Nuova Rivista di Neurologia
The Otolaryngologic Clinics of North America
Padiatrische Praxis
Revista – Hospital das Clinicas Faculdade de Medicina Universidade de Sao Paulo
Saishiu igaku
Science and Medicine

* *Partial indexing*

No additional articles were identified from the Cochrane Library. The search of Inside returned 19 applicable articles not identified from the other electronic databases. Of these 19 articles, 12 were reviews, one was a letter, two were technical articles, two were excluded as they provided insufficient data to construct a 2 × 2 table,[87,88] one[89] did not describe the gold standard method, and one included asymptomatic patients,[90] but was included in the carotid meta-analysis. The search of the Online Computer Library Centre returned 15 untitled articles not identified from the other electronic databases. None was included in the review: seven were reviews, one was a technical article, and the British Library could not trace the other seven.

Twenty-four journals were listed by Inside and the Online Computer Library Centre (*Box 1*) that were not indexed or were only partially indexed in the main bibliographic databases.

No article that had not been identified from elsewhere was found in the Internet search.

No additional relevant articles were retrieved by handsearching of the bibliographic lists of all articles passing the inclusion criteria. One hundred and five articles were found by handsearching of the ten key indexed journals. Of these 105 articles, 79 had already been retrieved using the main electronic search strategies, 23 were abstracts and two were not applicable (not on MRA). The remaining article[91] was missed by the electronic search strategies as it was indexed under the MeSH 'ultrasound' and contained only a limited amount of MRA data; it was eventually excluded from the review as

the MRA element of the study contained fewer than ten patients.

No article was excluded for reasons of language, but most non-English-language articles were excluded at the preliminary stages (see *Tables 2* and *3*). A further 32 articles were excluded at the final stage without full translation being necessary (see *Tables 5* and *7*). A full list of reasons for exclusion is given in chapter 5. One article, in Russian,[92] was read by a native speaker and found to satisfy all inclusion criteria. Three further articles[93–95] (two in German, one in French) satisfied all the inclusion criteria.

Outcomes and costs searches

The number of articles identified, retrieved and reviewed for resource use, cost or outcome data, is shown in *Table 9*. The majority of papers reported resource-use and utility data derived from expert opinion, and so were excluded. In addition, 43 articles reported resource-use and cost data that did not meet the inclusion criteria.

Articles included in the review

Descriptions of the articles included in the review are divided into those concerning carotid artery stenosis and those concerning peripheral vascular disease. Articles are described in a standard format comprising aims, methodology, follow-up, authors' conclusions, comparability and comments. Details of each article are tabulated in appendix 4, and these tables should be read together with the descriptions here. The tables in the appendix summarise data from the checklists, and the descriptions in this chapter give more information about these study design features.

The numerical sensitivity, specificity, positive predictive value, negative predictive value, accuracy, likelihood ratio and prevalence results calculated from data presented in each article are summarised separately in *Tables 10* to *16* for carotid artery stenosis and *Tables 17* to *23* for peripheral vascular disease. These numerical results are grouped by MRA technique in order to match the research questions raised in chapter 2.

Carotid artery stenosis

Ten articles from the carotid artery stenosis arm of the review satisfied all the inclusion criteria A–H. Some of these ten articles investigated more than one magnetic resonance technique: one article[96] used contrast-enhanced MRA techniques, five[94,97–100] used 3D TOF or phase-contrast techniques, and five[99,101–104] used 2D TOF or phase-contrast techniques. As these groups were too small for quantitative meta-analysis, the inclusion criteria were relaxed and a further 24 articles were included: One article[105] satisfied criteria A–G, six[90,106–110] satisfied A–F, four[111–114] satisfied A–E and 13[21,23,115–125] satisfied A–D. These 34 articles (see *Tables 10* to *16*), all of which satisfied criteria A–D (chapter 3), were included in the quantitative meta-analysis. The results are presented in chapter 6.

Articles satisfying all inclusion criteria A–H

The ten articles that satisfied all the inclusion criteria used contrast-enhanced MRA,[96] 3D TOF or phase-contrast MRA,[94,97–100] or 2D TOF or phase-contrast MRA.[99,101–104] Each of these studies is described below.

Contrast-enhanced MRA

Scarabino and co-workers[96]

Aims. To determine sensitivity, specificity and diagnostic accuracy of contrast-enhanced MRA compared to digital subtraction angiography in the study of carotid stenosis.

Methods.

- Prospective study.
- It is not stated whether observers were blinded to the clinical details of the patient or to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective common carotid DSA via a transfemoral approach.

Follow-up. Numbers proceeding to endarterectomy were provided, but no further follow-up was given.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is a potential for interpretation bias in this study as it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. Contrast-enhanced MRA has the same diagnostic accuracy as DSA.

Comments. Because this was one of only four articles[96,106,115,116] included in this review that involved the use of contrast-enhanced techniques in the assessment of carotid artery stenosis, the study data were not included in a quantitative meta-analysis in this review.

3D TOF or phase-contrast MRA

Chiesa and co-workers[97]

Aims. To compare 3D MRA with traditional angiography in the pre- and postoperative assessment of patients submitted to carotid endarterectomy and to establish its role in carotid artery surgery.

Methods.
- Prospective study.
- Observers blinded to the results of the DSA when interpreting MRA.
- Compared with selective intra-arterial carotid DSA.

Follow-up. The results of postoperative examinations were given. Morbidity and mortality were also discussed, but without reference to the time frame of follow-up.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

No details of the time elapsing between MRA and DSA examinations were given. However, disease progression bias was unlikely, as the examinations were being used as part of a preoperative assessment. There is a potential for interpretation bias in this study, as it is unclear from the description in the article if the results of MRA examinations were known to those interpreting the DSA findings.

Authors' conclusions. MRA is reliable for use if DSA is contraindicated.

Comments. Standard classifications of stenosis were not used in this study, so that results were not presented for 50–99% or 50–100%, and only data on the performance of MRA in distinguishing occluded from patent arteries could be included in the meta-analyses in this review. Although postoperative measurements were described in the paper, only the data from the preoperative assessments were used in this review.

Link and co-workers[94]

Aims. To assess the value of MRA in the sagittal technique compared to DSA in the evaluation of carotid artery stenosis.

Methods.
- Prospective study.
- It is not stated whether observers were blinded to the clinical details of the patient or to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial common carotid DSA.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is a potential for interpretation bias in this study, as it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. MRA gives a high degree of certainty for detecting candidates for surgery.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Magarelli and co-workers[98]

Aims. To determine whether increased diagnostic accuracy can be obtained by combining MRA and SCTA. To determine if more information is available for surgical decision-making by combining MRA and SCTA. To investigate the effect of limiting the role of DSA to cases in which the results of MRA and SCTA are inconsistent, especially in patients who are candidates for endarterectomy. To see if SCTA could play a role in the assessment of critical (> 70%) stenosis, where MRA may have a complete loss of signal within a segment with a less than 70% stenosis. Interobserver variability was also assessed.

Methods.
- Prospective study.
- Observers were blinded to the clinical details of the patient when interpreting MRA or DSA examinations. It is not stated whether observers

were blinded to other results when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial common carotid DSA.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is a potential for interpretation bias in this study as, although blinded to the clinical history of patients, it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. MRA is useful for identifying stenosis > 70% except where there are vascular loops, calcified plaque or very severe stenosis.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Scarabino and co-workers[99]
Aims. To compare the accuracy of three MRA techniques (2D TOF, 3D TOF, 3D phase contrast) in studying steno-occlusive disease of the carotid arteries.

Methods.
- Prospective study.
- Compared with selective DSA via transfemoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. No details of the sex distribution or age range of the study population were given, and there is therefore a potential for patient cohort bias. Interpretation biases may also be present, as observers were aware of the results of MRA when interpreting DSA examinations and it is unclear whether they were aware of the results of other tests or of the clinical details when interpreting MRA and DSA examinations.

Authors' conclusions. 3D TOF MRA is more reliable than 2D TOF or 3D phase-contrast MRA.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses for 2D TOF and 3D TOF methods in this review.

Uehara and co-workers[100]
Aims. To evaluate the usefulness and limits of 3D TOF MRA in the estimation of carotid artery bifurcation stenosis.

Methods.
- Prospective study.
- Observers were blinded to the clinical details of the patient when interpreting MRA or angiographic examinations. It is not stated whether observers were blinded to other results when interpreting MRA or angiographic examinations.
- Compared with selective arteriography via a femoral or brachial artery approach, using cut-film angiography or DSA.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is a potential for interpretation bias in this study as, although blinded to the clinical history of patients, it is unclear whether observers were aware of the results of other tests when interpreting MRA and angiographic examinations.

Authors' conclusions. 3D TOF MRA is good for selecting surgical candidates, but slow flow can mimic occlusion. The method could replace conventional angiography if surface detail or intracranial information is not required.

Comments. Data on the performance of MRA in distinguishing moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

2D TOF or phase-contrast MRA

Dadachanji and co-workers[101]
Aims. To evaluate the accuracy of MRA with a 2D TOF technique versus carotid angiography for screening of carotid disease.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective common carotid DSA via a transfemoral approach.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] There is potential for patient cohort bias since no details of the sex ratio, symptoms or co-morbid conditions of the study population were given. There is also potential for disease progression bias since the time lapse between MRA and DSA examinations was not stated.

Authors' conclusions. 2D TOF MRA should be used for screening, to exclude those not needing surgery. This recommendation was based on the finding that the severity of moderate stenoses was overestimated.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Huston and co-workers[102]
Aims. To determine the efficacy of 2D TOF MRA in characterising carotid stenosis, by using conventional angiography as the standard of reference, and to compare this type of MRA with ultrasound.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or angiographic examinations.
- Compared with selective arteriography via a femoral or brachial artery approach, using cut-film angiography or DSA.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

Authors' conclusions. Although accuracy was as good as for ultrasound, at the current state of development 2D TOF MRA cannot be considered a replacement for conventional angiography because of its insensitivity to ulceration and its limited field of view.

Comments. Data on the performance of MRA in distinguishing moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Laster and co-workers[103]
Aims. To assess the accuracy of MRA alone in screening for vascular stenosis of the common carotid bifurcation.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or angiographic examinations.
- Compared with selective common carotid arteriography via a transfemoral approach, using cut-film angiography or DSA.

Follow-up. No follow-up data were provided.

Comparability. This article is the only one that investigated over 200 vessels. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] There is potential for patient cohort bias since no details of the sex ratio, symptoms or co-morbid conditions of the study population were given. There is also potential for disease progression bias since the time lapse between MRA and angiographic examinations was not stated.

Authors' conclusions. 2D TOF MRA is recommended for screening to exclude candidates for surgery, possibly used in combination with ultrasound.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Scarabino and co-workers[99]
This study is described on page 32.

White and co-workers[104]
Aims. To determine the role and significance of MRA as an efficient, cost-effective screening examination for carotid artery stenosis.

Methods.
- Prospective study.
- It is not stated whether observers were blinded to the clinical details of the patient or to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial DSA via a femoral approach.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is a potential for interpretation bias in this study as it is unclear whether observers were aware of results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. 2D TOF MRA and duplex ultrasound are equally good for screening at the 40% stenosis level, with respectable sensitivity and specificity.

Comments. Because standard classifications of stenosis were not used in this study, only data on the performance of MRA in distinguishing occluded from patent arteries could be included in the meta-analyses in this review.

Articles satisfying final inclusion criteria A–G

One article satisfied final inclusion criteria A–G.[105]

3D TOF MRA

Sitzer and co-workers[105]
Aims. To assess the validity of non-invasive techniques for quantifying internal carotid stenosis with respect to the accepted standard of intra-arterial angiography.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests and to the clinical details of the patient when interpreting MRA or DSA examinations.
- Compared with selective common carotid DSA.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The study group was one of five that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is potential for disease progression bias as the study included some patients for whom the delay between MRA and DSA examinations was greater than 1 month. There is also potential for verification bias, as it is stated that four patients refused DSA.

Authors' conclusions. There is good correlation with DSA, but the appearance of the flow gap reduces the usefulness of 3D TOF MRA for precise quantification.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Articles satisfying final inclusion criteria A–F

Six articles[90,106–110] satisfied the inclusion criteria A–F. One used contrast-enhanced techniques,[106] two[107,108] used 3D TOF methods and three[90,109,110] used 2D TOF. All articles in this section have the potential for patient cohort bias as they included asymptomatic as well as symptomatic patients.

Contrast-enhanced MRA

Remonda and co-workers[106]
Aims. To determine the accuracy of Gd-enhanced 3D MRA in the evaluation of carotid artery stenosis.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial DSA via the femoral artery.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged

under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

Authors' conclusions. Although the study was statistically underpowered, contrast-enhanced MRA is an improvement over TOF MRA and should be used for screening.

Comments. Because this is one of only four articles[96,106,115,116] included in the review that involved the use of contrast-enhanced techniques in the assessment of carotid artery stenosis, data were not included in a quantitative meta-analysis.

3D TOF MRA

Ozaki and co-workers[107]

Aims. To determine whether clinically appropriate patients could be accurately selected for carotid endarterectomy based on MRA alone.

Methods.
- Retrospective study.
- It is not stated whether observers were blinded to the clinical details of the patient or to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial DSA.

Follow-up. No follow-up data were provided.

Comparability. The study population was unspecified both in terms of sex distribution and age range, and in terms of symptoms and clinical history. It is therefore likely that patient selection biases are present. There is a potential for interpretation bias in this study as it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations. Disease progression bias may also be present, as the study covers a 24-month period and no details were given of the time lapse between MRA and DSA examinations.

Authors' conclusions. The results of this study show low sensitivity and specificity compared with other published studies, and it is suggested by the authors in this article that publication bias could be the reason. The importance for surgical decisions of distinguishing occlusion from high-grade stenosis is emphasised.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) and moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Wilkerson and co-workers[108]

Aims. To place 3D carotid imaging in the proper perspective of non-invasive cerebrovascular examinations.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial DSA via the axillary or femoral approach.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

Disease progression bias may be present as the study was conducted over a 7-month period and no details of the time lapse between MRA and DSA examinations were given.

Authors' conclusions. The authors do not believe that 3D TOF MRA replaces duplex ultrasound scanning for non-invasive screening or conventional angiography for the definitive study. They recommend using it if the duplex results are uninterpretable.

Comments. Data on the performance of MRA in distinguishing moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

2D TOF MRA

Bianchi[90]

Aims. To compare the results of MRA and DSA in order to check the diagnostic accuracy of MRA in the selection of surgical carotid stenosis.

Methods.
- Prospective study.
- It is not stated whether observers were blinded to the clinical details of the patient or to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial DSA via a transfemoral approach.
- One of four articles[90,115–117] that considered image quality for identification of tandem lesions.

Follow-up. No follow-up data were provided.

Comparability. Notably, the study population was all male; the only other article reporting such a high proportion[123] contained 90% males. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124]

There is a potential for interpretation bias in this study as it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations. Although not all patients receiving DSA go on to receive MRA, withdrawal bias is less likely as it is stated that patients were 'randomly' selected to receive MRA.

Authors' conclusions. Using a 0.5 T field, 2D TOF MRA cannot replace conventional angiography in diagnosing 70–99% stenoses.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Drevet and co-workers[109]
Aims. To evaluate Doppler ultrasound, helical CT and MRA in the detection of carotid bifurcation atherosclerotic disease, and to compare these techniques with angiography.

Methods.
- Prospective study.
- It is not stated whether observers were blinded to the clinical details of the patient or to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective intra-arterial DSA via the transfemoral approach.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

There is a potential for interpretation bias in this study as it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. Both 2D TOF MRA and Doppler ultrasound should be used, proceeding to conventional angiography only if there is disagreement.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Riles and co-workers[110]
Aims. To determine the accuracy of MRA in assessing patients with cerebrovascular disease by comparing the results of conventional cerebral angiography, duplex scanning and MRA.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or DSA examinations.
- Compared with selective carotid DSA via the femoral or brachial arteries.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. Surgical procedures were performed and details of complications were given, but there was no indication of the time scale of follow-up.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. There is a potential for disease progression bias as the study includes patients with delays of up to 7 months between MRA and DSA examinations.

Authors' conclusions. 2D TOF MRA has limitations, especially in cases of occlusion, which were identified as severe stenosis, and overestimation of moderate stenosis.

Comments. Data on the performance of MRA in distinguishing moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Articles satisfying final inclusion criteria A–E

Four articles[111–114] satisfied inclusion criteria A–E. One of these[111] used 3D TOF MRA; the others used 2D TOF MRA. Articles satisfying only

criteria A–E gave no details of the method used to calculate the percentage stenosis of carotid arteries. All other results presented in the review were obtained from measurements made by the NASCET method, and the assumption is made that this was the method used in these articles too.

3D TOF MRA

Currie and co-workers[111]

Aims. To prospectively compare intra-arterial DSA and MRA assessment of internal carotid artery lesions in which no flow was detected by colour duplex.

Methods.
- Prospective study (April 1992 to October 1993, Bristol, UK).
- Observers were blinded to the results of DSA when interpreting MRA examinations.
- Compared with selective common carotid DSA.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. Biases associated with the application of the gold standard (DSA) may be present in this study, as some patients who received MRA did not go on to receive DSA, and the MRA examination was used as the basis for this decision. Disease progression bias may also be present, as the study was conducted over an 18-month period and no details of the time lapse between MRA and DSA examinations was given. Interpretation biases may have occurred, as it is unclear whether observers were aware of the results of MRA when interpreting DSA examinations. Similarly, it is unclear whether observers were aware of the results of Duplex ultrasound when interpreting other examinations.

Authors' conclusions. 3D TOF MRA complements duplex ultrasound, especially where flow is not detected using duplex scanning.

Comments. Data on the performance of MRA in distinguishing occluded from patent arteries were included in the meta-analyses in this review. Other results were not included because of the slightly different dichotomy used in this study (71–99%).

2D TOF MRA

Anson and co-workers[112]

Aims. To examine the accuracy of MRA compared with conventional angiography in symptomatic patients undergoing carotid endarterectomy and to compare the results with surgical findings.

Methods.
- Retrospective study.
- Observers were blinded to the results of other tests and to the clinical details of the patient when interpreting results of MRA or angiographic examinations.
- Compared with selective common carotid arteriography, using cut-film angiography or DSA.

Follow-up. A description was given of the surgical procedures performed, operative findings and postsurgical progress in some patients. However, no time scale for follow-up was provided.

Comparability. The study population was unspecified in terms of both sex distribution and age range.

Authors' conclusions. 2D TOF MRA is highly accurate and reliable for experienced reporters. It is potentially suitable as a sole test pre-operatively, and ought to replace duplex ultrasound for screening.

Comments. Data on the performance of MRA in distinguishing occluded from patent arteries were included in the meta-analyses in this review. Other results were not included because of the slightly different dichotomy used in this study (51–99%).

Litt and co-workers[113]

Aims. To use a 2D Fourier transform TOF technique to study patients with suspected carotid artery disease and compare the results with those obtained by using intra-arterial contrast angiography to evaluate the accuracy of MRA in imaging carotid artery stenosis.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests and to the clinical details of the patient when interpreting MRA or angiographic examinations.
- Compared with selective carotid arteriography via the femoral artery, using cut-film angiography or DSA.

Follow-up. No follow-up data were provided.

Comparability. The study group was one of five that had participants aged under

40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

No details of presenting symptoms or co-morbid conditions were provided. The study may therefore have included asymptomatic patients and patient cohort bias may be present. There is a potential for disease progression bias, as the study included patients with delays of up to 4 months between MRA and angiographic examinations.

Authors' conclusions. 2D TOF MRA is recommended for screening. Before it can be used as the definitive study, it must be possible to image the cavernous and petrous portions of the internal carotid artery.

Comments. Data on the performance of MRA in distinguishing moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Polak and co-workers[114]
Aims. To prospectively evaluate the findings obtained with 2D TOF angiography, as compared with angiography and Doppler sonography in patients with suspected carotid artery stenosis.

Methods.
- Prospective study.
- Observers were blinded to the results of DSA when interpreting MRA examinations.
- Compared with selective common carotid DSA via the femoral or brachial arteries.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. Biases associated with the application of the gold standard (DSA) may be present in this study, as some patients who received MRA did not go on to receive DSA, and the MRA examination was used as the basis for this decision. Interpretation biases may also be present, as it is unclear whether observers were aware of the results of MRA when interpreting DSA examinations. Similarly, it is unclear whether observers were aware of the results of duplex ultrasound when interpreting other examinations.

Authors' conclusions. 2D TOF MRA should be used together with duplex ultrasound. Only if discordant results are obtained should conventional angiography be performed. The authors found that MRA was operator independent.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Articles satisfying final inclusion criteria A–D

Thirteen articles[21,23,115–125] satisfied inclusion criteria A–D. Contrast-enhanced methods were used in two studies[115,116] 3D TOF or phase contrast in two studies[117,118] and 2D TOF or phase contrast in 11 studies.[21,23,116,117,119–125] Articles that satisfied only criteria A–D included the use of gold standard angiographic techniques other than selective intra-arterial angiography.

Contrast-enhanced MRA methods

Martinat and co-workers[115]
Aims. To evaluate the quality and reproducibility of Gd-enhanced 3D MRA for the study of supra-aortic vessels in patients presenting with cervical carotid stenosis.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests and to the clinical details of the patient when interpreting MRA and angiographic examinations.
- Compared with intra-arterial angiography, using aortic arch injection.
- One of four articles[90,115–117] that considered image quality for identification of tandem lesions.

Follow-up. No follow-up data were provided.

Comparability. The study group was one of five that had participants aged under 40 years.[105,113,115,120,124] No details of sex distribution, presenting symptoms or co-morbid conditions were given. The study may therefore have included asymptomatic patients and patient cohort bias may be present. Verification bias is likely as some patients who received MRA did not go on to receive angiography, and it is unclear whether the MRA examination was used as the basis for this decision. There is also a potential for disease progression bias, as the study was conducted over a 6-month period and no

details of the time lapse between MRA and angiographic examinations was given.

Authors' conclusions. There was good agreement with conventional angiography, but a tendency for overestimation of moderate stenoses. Flow artefacts are avoided using contrast-enhanced MRA. Gd-enhanced 3D MRA is an alternative to conventional angiography.

Comments. Because this is one of only four articles[96,106,115,116] included in the review that involves the use of contrast-enhanced techniques in the assessment of carotid artery stenosis, data were not included in a quantitative meta-analysis.

Sardanelli and co-workers[116]
Aims. To compare Gd-enhanced breath-hold fast imaging with steady-state precession (Gd FISP) with unenhanced TOF sequences in evaluating internal carotid arteries.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with DSA, using aortic arch injection.
- One of four articles[90,115–117] that considered image quality for identification of tandem lesions.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

Authors' conclusions. Gd-enhanced MRA is an interesting, largely artefact-free improvement over TOF methods. It should be substituted for unenhanced techniques, and be used with duplex ultrasound for screening and for evaluation of symptomatic individuals.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the 2D TOF and 3D TOF meta-analyses in this review. Because this is one of only four articles[96,106,115,116] included in the review that involves the use of contrast-enhanced techniques in the assessment of carotid artery stenosis, the 3D contrast-enhanced MRA data were not included in a quantitative meta-analysis.

3D TOF or phase-contrast methods

Fellner and co-workers[117]
Aims. To determine the value of a dedicated coil in covering the patient's head and neck for MRA of the supra-aortic arteries using 2D fast low angle shot (FLASH), 3D FISP and 3D tilted optimised non-saturating excitation (TONE) MRA.

Methods.
- Prospective study.
- Observers were blinded to the results of DSA when interpreting MRA examinations.
- Compared with intra-arterial DSA, using aortic arch injection.
- One of four articles[90,115–117] that considered image quality for identification of tandem lesions.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. No details of presenting symptoms or co-morbid conditions were provided. The study may therefore have included asymptomatic patients and patient cohort bias may be present. There is a potential for disease progression bias, as no details of the time lapse between MRA and DSA examinations were given. Interpretation biases may also be present, as it is unclear whether observers were aware of the results of MRA when interpreting DSA examinations. Similarly, it is unclear whether observers were aware of the results of duplex ultrasound when interpreting other examinations.

Authors' conclusions. Sensitivity and specificity were similar for all three techniques using a dedicated head and neck coil. Image quality at the aortic arch needs further improvement.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses for both 2D and 3D TOF methods in this review.

Mattle and co-workers[118]
Aims. To investigate the accuracy of MRI for the detection of extracranial carotid stenoses by

correlating 'bright blood' and 'black blood' images with duplex scan and conventional angiography.

Methods.
- Retrospective study.
- Compared with DSA or cut-film angiography.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. Numbers proceeding to endarterectomy were given, but there was no further follow-up.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. The study included asymptomatic patients (35%) and may therefore have been subject to patient cohort bias. Verification bias is likely, as some patients who received MRA did not go on to receive angiography, and it is unclear whether the MRA examination was used as the basis for this decision. Interpretation biases may also be present, as it is unclear whether observers were aware of the results of other tests when interpreting MRA and angiographic examinations.

Authors' conclusions. When there was agreement between the MRA and duplex results, there was 100% correlation with conventional angiography. In patients for whom conventional angiography is high risk, MRA and duplex imaging should be used.

Comments. Data on the performance of MRA were not included in the meta-analyses in this review because only two articles[23,118] made diagnoses based on viewing both 2D and 3D TOF images together. The results are given in *Tables 11* and *13*.

Sardanelli and co-workers[116]
This study is discussed on page 39.

2D TOF or phase-contrast methods

Buijs and co-workers[119]
Aims. To evaluate the clinical efficacy of the 2D TOF MRA technique in imaging the carotid bifurcation in patients and volunteers as compared to contrast angiography and pulsed and colour Doppler ultrasound.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA or DSA examinations.
- 2D TOF MRA using a 1.5 T Philips Gyroscan S15 system and a head/neck coil.
- Intravenous DSA.
- Did not classify degree of stenosis by the NASCET or ECST method.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was not given and the study included asymptomatic patients. Patient cohort bias may therefore be present. Biases associated with the application of the gold standard (DSA) may be present, as some patients who received MRA did not go on to receive DSA, and it is unclear whether the MRA examination was used as the basis for this decision. Furthermore, intravenous DSA was employed rather than an intra-arterial technique. Disease progression bias is likely as a time lapse of up to 1.5 years between MRA and DSA examinations was reported.

Authors' conclusions. At present 2D TOF MRA is not clinically useful for diagnosing the degree of carotid artery stenosis. In particular, it may overestimate moderate stenoses.

Comments. Because standard classifications of stenosis were not used in this study, only data on the performance of MRA in distinguishing occluded from patent arteries could be included in the meta-analyses in this review.

Fellner and co-workers[117]
This study is discussed on page 39.

Heiserman and co-workers[120]
Aims. To investigate the clinical efficacy of a 2D TOF MRA protocol in characterising carotid artery narrowing.

Methods.
- Retrospective study.
- Observers were blinded to the results of other tests and to the clinical details of the patient when interpreting MRA and angiography examinations.
- Compared with intra-arterial DSA or cut-film angiography.

Follow-up. No follow-up data were provided.

Comparability. The study group was one of five that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

Some details of presenting symptoms but not of co-morbid conditions were provided. The study may therefore have included asymptomatic patients and patient cohort bias may be present.

Authors' conclusions. 2D TOF MRA is a robust and accurate modality for evaluation of atherosclerotic narrowing of the carotid artery bifurcation. At present conventional angiography is indicated prior to surgery to exclude tandem lesions.

Comments. Data on the performance of MRA in distinguishing occluded from patent arteries were included in the meta-analyses in this review. Other results were not included because of the slightly different dichotomy used in this study (51–99%).

Kido and co-workers[121]
Aims. To evaluate the sensitivity and specificity of two MRA techniques used together, compared with invasive angiography in the identification of clinically significant stenosis of the carotid artery near the bifurcation.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests and to the clinical details of the patient when interpreting MRA examinations.
- Compared with intra-arterial or intravenous DSA or cut-film angiography.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable to that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. No details of presenting symptoms or co-morbid conditions were provided. The study may therefore have included asymptomatic patients and patient cohort bias may be present. Diagnostic review bias may also be present, as it is unclear whether observers were aware of the results of other tests when interpreting angiographic examinations. Biases associated with the application of the gold standard may have also occurred, since a proportion of patients underwent intravenous DSA.

Authors' conclusions. The sensitivity and specificity are lower than for conventional angiography. Experienced users do better.

Comments. Data on the performance of MRA in distinguishing moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Nicholas and co-workers[122]
Aims. To determine whether non-invasive evaluation with duplex ultrasonography and MRA of patients with carotid artery stenosis can replace contrast angiography at the authors' institution.

Methods.
- Retrospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with aortic arch or selective carotid catheterisation, using cut-film angiography or DSA.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. Asymptomatic patients (37%) were included and patient cohort bias may therefore be present. There is also a potential for disease progression bias, as the study was conducted over a period of 2 years and 4 months and no details of the time lapse between MRA and angiographic examinations was given.

Authors' conclusions. When duplex and MRA results are concordant, conventional angiography need not be performed prior to surgery

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) and moderately stenosed (50–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Pavone and co-workers[123]
Aims. To evaluate carotid arteries by means of 2D TOF MRA with a low field strength magnet and to compare the findings with those of DSA.

Methods.
- Prospective study.
- Observers were blinded to the results of DSA when interpreting MRA examinations.
- Compared with DSA, using aortic arch injection.

Follow-up. No follow-up data were provided.

Comparability. The sex distribution was 90% male, comparable with only one other article[90] where the value was 100%. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] No details of presenting symptoms or co-morbid conditions were given. The study may therefore have included asymptomatic patients and patient cohort bias may be present. As it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations, and interpretation biases may have occurred. There is also a potential for verification bias, as it is unclear whether all patients receiving MRA also received DSA examinations.

Authors' conclusions. Low field strength MRA could have the same clinical value as MRA performed with high field strengths. No severe stenosis was overestimated as an occlusion.

Comments. Data on the performance of MRA in distinguishing occluded from patent arteries were included in the meta-analyses in this review. Other results were not included because of the slightly different dichotomy used in this study (71–99%).

Pavone and co-workers[124]
Aims. To assess the clinical value of MRA in the evaluation of carotid arteries at low field strength.

Methods.
- Prospective study.
- Observers were blinded to the results of the other test when interpreting MRA and DSA examinations.
- Compared with DSA, using aortic arch injection.

Follow-up. No follow-up data were provided.

Comparability. The study group was one of five that had participants aged under 40 years.[105,113,115,120,124] No details of sex distribution, presenting symptoms or co-morbid conditions were given. The study may therefore have included asymptomatic patients and patient cohort bias may be present. As no details of the time period over which the study was conducted or of the time lapse between MRA and DSA examinations were given, disease progression bias may also be present.

Authors' conclusions. There was high agreement between DSA and MRA results, even at low field strength.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Sardanelli and co-workers[116]
This study is discussed on page 39.

Spartera and co-workers[125]
Aims. To compare DSA and duplex scanning with 2D MRA in order to evaluate the accuracy of MRA in determining carotid stenosis.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with DSA, using aortic arch injection.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. No details of the age and sex distribution of the study population were given. The study included asymptomatic (12%) patients and patient cohort bias is therefore likely.

Authors' conclusions. 2D MRA alone is not a reliable method for evaluating the presence of carotid artery stenosis. It is a substitute for conventional angiography only when there are convoluted arteries or contrast medium is contraindicated.

Comments. Because standard classifications of stenosis were not used in this study, only data on the performance of MRA in distinguishing occluded from patent arteries could be included in the meta-analyses in this review.

Turnipseed and co-workers[21]
Aims. To prospectively evaluate the use of duplex imaging and MRA in the diagnosis and management of patients with symptomatic carotid artery disease.

Methods.
- Prospective study.
- Compared with DSA. No technical details given.

- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. Details of surgical procedures and postoperative morbidity and mortality were provided, but no time scale of follow-up was given.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value. Verification bias is likely, as not all patients receiving MRA went on to receive DSA, and the result of the MRA examination was used to decide which patients received DSA. As it is unclear whether observers were aware of the results of other tests or the clinical details of patients when interpreting MRA and DSA examinations, interpretation biases may have occurred. There is also potential for disease progression bias, as no details of the time period over which the study was conducted or of the time lapse between MRA and DSA examinations were given.

Authors' conclusions. Conventional angiography may not be required to select patients for surgery when concordant results are obtained from duplex imaging and MRA.

Comments. Data on the performance of MRA in distinguishing severely stenosed (70–99%) arteries from patent and occluded arteries, and occluded from patent arteries, were included in the meta-analyses in this review.

Young and co-workers[23]

Aims. To measure the level of agreement between MRA, intra-arterial DSA and duplex ultrasound in determining the degree of stenosis of the internal carotid artery, at or around the carotid bifurcation, in patients under consideration for prophylactic carotid endarterectomy.

Methods.

- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with DSA, using selective carotid or aortic arch catheterisation.
- Uses the Bland and Altman[126] method for comparing differences between measurements.
- One of the 14 articles[21,23,102,104,105,108–111,114,118,119,122,125] that also evaluated duplex ultrasound.

Follow-up. No follow-up data were provided.

Comparability. The age range of the study group was comparable with that in most other reports, except for five studies that had participants aged under 40 years.[105,113,115,120,124] The sex distribution was over 50% male, as was the case for all other articles reporting a value.

Authors' conclusions. Reliable conclusions for recommending carotid endarterectomy can be made on the basis of non-invasive imaging alone, if duplex and MRA results agree.

Comments. Data on the performance of MRA were not included in the meta-analyses in this review because only two articles[23,118] made diagnoses based on viewing both 2D and 3D TOF images together. The results are given in *Tables 14* and *16*.

Summary

The 34 articles represent studies on a range of patient populations, and this means that any conclusion drawn by combining their results should be treated cautiously. Patient numbers ranged from 11 to 131 (mean = 42). The number with a stenosis in the relevant range was small in almost all studies (see *Tables 10* to *16*). In the articles where sex distribution was reported, the majority of patients were, in all but one case, male; in these articles the proportion of male patients ranged from 55% to 100% (mean = 69%). Nine articles[99,101,103,107,112,115,119,124,125] did not report the sex distribution. The lower limit for patient age ranged from 6 to 63 years (mean = 41 years), and the upper limit ranged from 73 to 89 years (mean = 80 years). Nine articles did not report the age range.[21,98,99,107,111,112,118,119,125] Twelve articles stated that asymptomatic patients were included,[23,90,106–110,114,118,119,122,125] and a further 16 articles gave no information about patient symptoms.[94,96–99,101,103,105,113,115–117,121–124]

It is noticeable that confidence in the technique has increased over the years. The conclusions drawn by authors of the earliest articles are cautious, and they often refer to the promise of the technique and the potential for improvement in image quality by using future developments. Many authors are clearly reporting a study the results of which have already been superseded, and they mention the new equipment that they are using in practice. Whether or not the numerical diagnostic performance has increased with time is investigated in chapter 7. The early authors tended to recommend MRA for screening prior to conventional angiography; in such an application false-positive diagnoses are less undesirable. Alternatively, they recommend using a combination of MRA and duplex

ultrasound. More recent articles, where 3D TOF or contrast-enhanced techniques were used, are considerably more confident, especially with regard to contrast-enhanced techniques.

Follow-up was rare, and when information was provided there was no indication of time scale. These observations justify our decision to use a modelling approach to address our question on the long-term costs and outcomes of MRA and DSA in the diagnosis and management of patients presenting with carotid arterial disease.

In chapter 6 the results from these articles have been combined using SROC analysis, to give quantitative summary estimates of performance for each MRA technique at the three dichotomies (0–69% or 100% versus 70–99%; 0–49% or 100% versus 50–99%; 0–99% versus 100%.). In chapter 7 we assess numerically some of the qualitative observations made above to investigate the effect of study year, MRA technique and validity. A fuller discussion is given in chapter 8.

Peripheral vascular disease

Twenty articles[37,82,92,93,95,127–141] from the peripheral vascular disease part of the review satisfied all the final inclusion criteria. Where results from these articles exactly fitted the dichotomies for our quantitative meta-analyses, they were included in the analyses, and results are given in chapter 6. The main features of each article are described qualitatively below (for quantitative results see *Tables 17* to *23*).

Eight studies used contrast-enhanced MRA.[37,95,128,133,135,136,139,140] Of these, only one[133] used 2D rather than 3D contrast-enhanced MRA, and one[128] also used non-enhanced 3D TOF MRA. Thirteen studies[82,92,93,127,129–132,134,135,137,138,141] used 2D TOF or phase-contrast MRA.

Contrast-enhanced MRA

Cortell and co-workers[128]

Aims. To compare peripheral vascular MRA done with a standard transmit–receive head coil with conventional arteriography for identifying and evaluating run-off vessels below the knee.

Methods.
- Retrospective study.
- Observers were blinded to the results of other tests and to the clinical details of patients when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film angiography or DSA, with femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers,[133] and a comparable sex distribution, except for those in the reports by Laissy and co-workers[133] and Sueyoshi and co-workers.[139] The contrast-enhanced MRA part of this article cannot be compared with the others using contrast-enhanced MRA, as contrast was used only above the knee and only when deemed appropriate by the monitoring physician. The non-contrast-enhanced MRA part of the study was the only 3D TOF study included in the review.

Authors' conclusions. Peripheral vascular MRA is a highly sensitive and specific way to evaluate below-knee run-off, providing information comparable to that obtained from conventional angiography.

Comments. Non-contrast-enhanced MRA data from this article could not be included in a meta-analysis in this review, as it was the only article using 3D TOF MRA techniques that was included. Nor could the data be included in the contrast-enhanced MRA meta-analysis, as the results for patients in whom contrast-enhanced MRA had been used could not be separated from those in whom it had not.

Laissy and co-workers[133]

Aims. To assess the diagnostic value of 2D subtraction MRA of lower extremities in patients with symptomatic peripheral arterial occlusive disease, with conventional angiography as the standard reference.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film angiography, using femoral or brachial catheterisation.

Follow-up. No follow-up data were provided.

Comparability. This was the only contrast-enhanced MRA article using 2D rather than 3D techniques. The patient group was younger than in the other contrast-enhanced MRA articles, and the high male ratio in this study is comparable only with that in

the study by Sueyoshi and co-workers.[139] The iliac arteries were not investigated. As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present.

Authors' conclusions. Two-dimensional subtraction MRA provides comparable information to that obtained with conventional angiography, especially in patients without rest pain.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries were included in the meta-analyses in this review.

Meaney and co-workers[37]
Aims. To compare stepping-table digital subtraction Gd-enhanced MRA of the distal aorta and lower extremity arteries with conventional catheter digital subtraction X-ray angiography in patients with arterio-occlusive disease.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with intra-arterial DSA, using selective distal aorta catheterisation at the level of the fourth lumbar vertebra, with femoral insertion.

Follow-up. No follow-up data were provided.

Comparability. This was the only contrast-enhanced MRA study to use a stepping-table technique to facilitate the multiple acquisitions. The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers,[133] and a comparable sex distribution, except for those in the reports by Laissy and co-workers[133] and Sueyoshi and co-workers.[139]

Authors' conclusions. Stepping-table digital subtraction Gd-enhanced MRA was highly accurate compared with catheter angiography in patients with arterio-occlusive disease of the aorta and outflow vessels. The sensitivity and specificity were 81% and 91% (observer 1) and 89% and 95% (observer 2).

Comments. Data on the performance of MRA in distinguishing occluded (100%) from patent arteries were included in the meta-analyses in this review. A slightly different dichotomy was used in this study (51–99%), and at this dichotomy insufficient data were presented in the article for construction of a 2 × 2 table, so these results could not included in the meta-analysis.

Perrier and co-workers[95]
Aims. To compare contrast-enhanced MRA with conventional angiography in the evaluation of the iliac and femoral arteries.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film angiography, with femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers,[133] and a comparable sex distribution, except for those in the reports by Laissy and co-workers[133] and Sueyoshi and co-workers.[139] Only vessels above the knee were included, and in this respect the study is similar to the one by Quinn and co-workers.[135] As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present.

Authors' conclusions. The results of contrast-enhanced MRA were in good agreement with those from conventional angiography, except for the internal iliac arteries and deep femoral arteries. Contrast-enhanced MRA is not therefore an alternative to conventional angiography.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries were included in the meta-analyses in this review.

Quinn and co-workers[135]
Aims. To compare the diagnostic efficacy of dynamic contrast-enhanced 3D TOF MRA with 2D TOF MRA with cardiac compensated fast gradient recalled echo angiography and conventional angiography, when available.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film angiography, with femoral catheterisation.

Follow-up. Surgical procedures suggested by conventional angiography, and 2D and 3D TOF MRA were reported independently. No details of the procedures performed or further follow-up were given.

Comparability. The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers,[133] and a comparable sex distribution, except for those in the reports by Laissy and co-workers[133] and Sueyoshi and co-workers.[139] Only vessels above the knee were included, and in this respect the article is most similar to the one by Perrier and co-workers.[95] It is a small study, like the one by Rofsky and co-workers.[136] It is unusual in stating the number of normal segments that were included, as did only three other reports[135,139,140] in the contrast-enhanced MRA group. As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present. Biases associated with the application of the gold standard may also be present, as not all patients receiving MRA went on to receive angiography, since the result of the MRA examination was used to determine which patients received angiography.

Authors' conclusions. There was high interobserver agreement and diagnostic efficacy for both 3D contrast-enhanced MRA and 2D TOF MRA. The worst performance was for 2D TOF MRA in external iliac arteries. Contrast-enhanced MRA should be reserved for situations where iliac vessels are extremely tortuous or occluded, or external iliac arteries are poorly seen.

Comments. Data on the performance of both 3D contrast-enhanced MRA and 2D TOF MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Rofsky and co-workers[136]

Aims. To demonstrate the utility of low-dose Gd-enhanced MRA of two consecutive anatomic areas for the assessment of peripheral vascular disease.

Methods.

- Prospective study.
- Compared with intra-arterial DSA, using selective abdominal aorta or iliac artery catheterisation.

Follow-up. No follow-up data were provided.

Comparability. This article describes a study using lower doses of contrast agent than the other contrast-enhanced MRA articles included in the review. The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers,[133] and a comparable sex distribution, except for those in the reports by Laissy and co-workers[133] and Sueyoshi and co-workers.[139] It was a small study, like the one by Quinn and co-workers.[135] Interpretation biases may be present, as it is unclear whether observers were aware of the results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. Lower doses of contrast material may be used to evaluate peripheral vascular disease. Reduced examination times makes it more feasible to examine multiple anatomical areas.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries were included in the meta-analyses in this review.

Sueyoshi and co-workers[139]

Aims. To determine the clinical feasibility of 3D dynamic contrast-agent-enhanced subtraction MRA in patients with symptoms of lower extremity ischaemia.

Methods.

- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial DSA or cut-film arteriography, with femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. The high male ratio in the patient group is comparable only to that in the study by Laissy and co-workers.[133] The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers.[133] It is unusual in stating the number of normal segments that were included, as did only three other articles[135,139,140] in the contrast-enhanced MRA group.

Authors' conclusions. The technique showed high sensitivity and specificity. It is a rapid technique which can be used as an alternative to conventional angiography for screening. Only limited information about the character of vessel walls and flow dynamics can be provided.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries were included in the meta-analyses in this review.

Winterer and co-workers[140]
Aims. To evaluate the feasibility and clinical use of MRA for examining the pelvic and lower limb arteries in patients with arterial occlusive disease.

Methods.
- Prospective study.
- Compared with intra-arterial DSA, using femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. The study included many more segments than did the other contrast-enhanced MRA studies, but a large proportion of these were normal segments. The article is unusual in stating the number of normal segments that were included, as did only three other articles[135,139,140] in the contrast-enhanced MRA group. The patient group had a comparable age range to that in the other contrast-enhanced MRA articles, except for the one by Laissy and co-workers,[133] and a comparable sex distribution, except for those in the reports by Laissy and co-workers[133] and Sueyoshi and co-workers.[139] As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present. Interpretation biases may also be present since, although observers were blinded to the results of MRA when interpreting DSA examinations, it is unclear whether they were aware of the results of other tests when interpreting MRA and DSA examinations.

Authors' conclusions. MRA has great potential for use in the primary diagnosis of peripheral arterial occlusive disease. The authors noted that their group had a high prevalence of disease.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries were included in the meta-analyses in this review.

3D TOF MRA

Cortell and co-workers[128]
This study is described on page 44.

2D TOF MRA

Baumgartner and co-workers[93]
Aims. To prospectively compare duplex sonography, MRA and contrast-enhanced arteriography for the assessment of peripheral vascular occlusive disease.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film angiography or DSA.
- Duplex sonography was also studied.

Follow-up. No follow-up data were provided.

Comparability. Above-knee vessels were studied, in common with ten other articles.[92,93,127,131,132,134,135,137,138,141] No normal vessel segments were included in the results, which was also the case in three other reports.[93,138,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] Interpretation biases may be present as, although observers were blinded to the results of angiography when interpreting MRA examinations, it is unclear whether they were aware of the results of other tests when interpreting MRA and angiographic examinations.

Authors' conclusions. Signal voids due to low resolution and flow changes may limit the diagnosis of occlusions.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Carpenter and co-workers[127]
Aims. To determine whether MRA could accurately define the anatomy of the aorta, iliac and femoral arteries.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film angiography or DSA, using femoral catheterisation.

Follow-up. Details of the procedures performed were given, but no further follow-up information was provided.

Comparability. Above-knee vessels were studied, as in ten other reports.[92,93,127,131,132,134,135,137,138,141] The patient group had a larger age range than in the other 2D TOF studies. The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] Forty-five per cent of the study group were diabetic. The number of normal segments included in the analysis was more than zero and this was stated, as it was in four other articles[127,129,130,134] in the 2D TOF group. As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present.

Authors' conclusions. The results obtained with MRA are comparable to those obtained with conventional angiography, both proximally and superior distally.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Davis and co-workers[129]

Aims. To evaluate the feasibility of using MRA for following up patients who have undergone interventional therapy of the infrapopliteal vascular bed.

Methods.

- Prospective study.
- Observers were blinded to the results of other tests and to the clinical details of patients when interpreting MRA and DSA examinations.
- Compared with intra-arterial DSA, using femoral catheterisation.

Follow-up. Data on stenosis before and after percutaneous transluminal angioplasty were reported, but no further follow-up data were provided.

Comparability. The majority of the study group was female, and this is the only 2D TOF article for which this was the case. Below-knee vessels were studied, as in five other studies.[82,129,130,137,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The number of normal segments included in the analysis was more than zero, and this was stated, as it was in four other articles[127,129,130,134] in the 2D TOF group. As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present.

Authors' conclusions. MRA was highly sensitive and specific for the detection of significant stenosis when compared with DSA. A greater number of patent vessel segments could be identified using MRA than using DSA. Therapy-induced changes were equally well depicted by both methods.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review. Only preinterventional data were included in the meta-analyses

Eklof and co-workers[130]

Aims. To compare 2D inflow MRA with selective X-ray angiography in patients with severe chronic leg ischaemia.

Methods.

- Prospective study.
- Observers were blinded to the results of other tests and to the clinical details of patients when interpreting MRA and X-ray angiography examinations.
- Compared with intra-arterial X-ray angiography, using femoral catheterisation (DSA).

Follow-up. No follow-up data were provided.

Comparability. The severity of symptoms were greater in this study, with 96% of the group suffering from critical ischaemia. This article is least comparable with the three articles where all patients had claudication.[92,131,138] Below-knee vessels were studied, as was the case in five other articles in this group.[82,129,130,137,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] The number of normal segments included in the analysis was more than zero, and this was stated, as it was for four other articles[127,129,130,134] in the 2D TOF group. Biases associated with the application of the gold standard may also be present, as not all patients

receiving MRA went on to receive X-ray angiography, and the result of the MRA examination was used to determine which patients received X-ray angiography.

Authors' conclusions. There was good agreement between the results of MRA and those from X-ray angiography for the calf, but not for the foot.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries for calf vessels were included in the meta-analyses in this review.

Ho and co-workers[131]
Aims. To compare two inflow MRA pulse sequences obtained without systolic synchronisation and to compare these two MRA pulse sequences with conventional angiography.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and X-ray angiography examinations.
- Compared with intra-arterial cut-film angiography, using femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. All patients had claudication, which was the case in three other studies.[92,131,138] Above-knee vessels were studied, as was the case in ten other studies.[92,93,127,131,132,134,135,137,138,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present. Biases associated with the application of the gold standard may also be present, as not all patients who received MRA went on to receive X-ray angiography, and it is unclear whether the result of the MRA examination was used to determine which patients received X-ray angiography.

Authors' conclusions. Systolic synchronisation of MRA improves image contrast and quality, and is essential in assessing the pelvic and upper femoral arteries.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Hoch and co-workers[82]
Aims. To determine whether MRA will allow preoperative management decisions to be made without the need for contrast arteriography in patients with lower extremity ischaemia caused by infrainguinal arterial occlusive disease.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with intra-arterial DSA, using femoral catheterisation.

Follow-up. Revascularisation plans based on MRA and DSA were formulated independently. Where these plans differed they were reported in the article. The number and type of surgical procedures carried out were also reported, but no further follow-up information was provided.

Comparability. Below-knee vessels were studied, as was the case in five other studies.[82,129,130,137,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present.

Authors' conclusions. Despite the modest sensitivity of MRA in diagnosing stenoses, the mismatches between MRA and DSA did not adversely affect the authors' ability to plan the appropriate clinical management. When used in combination with the patient's physical examination and segmental limb pressures, MRA is sufficient for planning infrainguinal arterial bypass procedures and selecting patients for percutaneous transluminal angioplasty.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Laissy and co-workers[132]
Aims. To assess the efficacy of MRA of iliac arteries before and immediately after percutaneous transluminal angioplasty.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with intra-arterial DSA, using iliac catheterisation.

Follow-up. The results of percutaneous transluminal angioplasty were reported, but no further follow-up information was provided.

Comparability. Above-knee vessels were studied, as was the case in ten other studies.[92,93,127,131,132,134,135,137,138,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129]

Authors' conclusions. MRA can help localise significant iliac stenoses.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries before percutaneous transluminal angioplasty were included in the meta-analyses in this review.

Mulligan and co-workers[134]
Aims. To compare the usefulness of colour duplex ultrasound and MRA in the detection and grading of arterial stenosis and occlusion, and to determine revascularisation procedures with data from colour duplex ultrasound and MRA.

Methods.
- Prospective study.
- Compared with intra-arterial angiography, via femoral, transaxillary or translumbar catheterisation.

Follow-up. Surgical procedures suggested by conventional angiography, colour duplex ultrasound and MRA were reported independently. No details were given of the procedures performed or of further follow-up.

Comparability. This was an early study, starting in 1989. The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The study population was 100% male, as was the case in the study by Timonina and co-workers.[92] Above-knee vessels were studied, as was the case in ten other studies.[92,93,127,131,132,134,135,137,138,141] The number of normal segments included in the analysis was more than zero, and this was stated, as it was in four other articles[127,129,130,134] in the 2D TOF group. Interpretation biases may be present, as observers were aware of the results of angiography when interpreting MRA examinations. It is unclear whether the observers were aware of the results of other tests when interpreting MRA and angiographic examinations.

Authors' conclusions. The authors did not strongly recommend the use of MRA in the peripheral vasculature, recommending further studies to improve the technique.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Quinn and co-workers[135]
This study is discussed on page 45.

Snidow and co-workers[137]
Aims. To determine the frequency with which treatment plans based on findings at MRA match those based on findings at conventional X-ray arteriography in the evaluation of symptomatic lower extremity ischaemia.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with intra-arterial X-ray angiography, using abdominal aorta or femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. Above-knee vessels were studied, as was the case in ten other studies,[92,93,127,131,132,134,135,137,138,141] and below-knee vessels were studied, as was the case in five other studies.[82,129,130,137,141] The majority (95%) of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] With 95% of the group being male, the study is similar to the two studies in which the study group was

100% male.[92,134] As the criteria used to select patients for inclusion in the study were unclear and no details of the age range, presenting symptoms or clinical history of the included patients were given, it is likely that patient selection biases are present.

Authors' conclusions. For evaluation of symptomatic lower extremity ischaemia, 2D TOF MRA cannot be considered a reliable substitute for X-ray angiography in patients who lack contraindications to X-ray angiography. The major shortcoming of MRA was its lack of specificity, especially in the evaluation of iliac arteries.

Comments. Data on the performance of MRA in distinguishing severely stenosed and occluded (50–100%) from patent arteries were included in the meta-analyses in this review.

Steffens and co-workers[138]
Aims. To evaluate the authors' capability to use coronally acquired, cardiac-gated 2D phase-contrast MRA to correctly detect and grade atherosclerotic lesions from the aortic bifurcation to the popliteal artery.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and DSA examinations.
- Compared with intra-arterial DSA, using aorta catheterisation level with the first lumbar vertebra.

Follow-up. No follow-up data were provided.

Comparability. This was the only study that used phase-contrast methods. All patients had claudication, which was the case in three other studies.[92,131,138] Above-knee vessels were studied, as was the case in ten other studies.[92,93,127,131,132,134,135,137,138,141] No normal vessel segments were included in the results, which was the case in three other studies.[93,138,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] As the sex distribution of patients included in the study was not reported, patient cohort bias may be present.

Authors' conclusions. Coronally acquired, cardiac-gated 2D phase-contrast MRA has good sensitivity and specificity in the iliac, femoral and popliteal arteries. Its value in evaluating more distal arteries needs further study.

Comments. Data from this study could not be included in the meta-analyses in this review as no other articles that used phase-contrast MRA techniques, which satisfied all inclusion criteria, were available.

Timonina and co-workers[92]
Aims. To compare the results of 2D TOF MRA with data from conventional contrast arteriography for the assessment of stenotic and occlusive lesions of the arteries of the lower extremities in patients with intermittent claudication.

Methods.
- Prospective study.
- Compared with intra-arterial X-ray angiography, using femoral catheterisation.

Follow-up. No follow-up data were provided.

Comparability. The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers,[127] but included only male patients, as was the case in the study by Mulligan and co-workers.[134] All patients had claudication, which was also the case in three other studies.[92,131,138] Above-knee vessels were studied, as was the case in ten other studies.[92,93,127,131,132,134,135,137,138,141] As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present. Interpretation biases may also be present, as it is unclear whether observers were aware of the results of other tests when interpreting MRA and X-ray angiography examinations.

Authors' conclusions. MRA appeared to be a highly informative technique for the diagnosis of stenoses and occlusions of arteries of the lower extremities.

Comments. Data on the performance of MRA in distinguishing occluded (100%) from patent arteries were included in the meta-analyses in this review.

Yucel and co-workers[141]
Aims. To evaluate 2D TOF MRA in comparison with conventional arteriography in the assessment of arteriosclerotic occlusive disease of the iliac, femoral and popliteal arteries.

Methods.
- Prospective study.
- Observers were blinded to the results of other tests when interpreting MRA and angiographic examinations.
- Compared with intra-arterial cut-film arteriography.

Follow-up. No follow-up data were provided.

Comparability. No normal vessel segments were included in the results, which was also the case in three other studies.[93,138,141] The patient group had a comparable age range to that in the other 2D TOF studies, except the one by Carpenter and co-workers.[127] The majority of patients were male, which is similar to the case in the other 2D TOF studies, except the one by Davis and co-workers.[129] As the criteria used to select patients for inclusion in the study were unclear, patient filtering biases may be present.

Authors' conclusions. MRA shows promise, but its limitations include decreased accuracy in the iliac segment, and problems in optimising the method in the tibial arteries. It may be a substitute for conventional arteriography in patients with contraindications to this, when combined with correlative haemodynamic evaluation.

Comments. Data on the performance of MRA in distinguishing severely stenosed (50–99%) arteries from patent and occluded arteries, severely stenosed and occluded (50–100%) from patent arteries, and occluded (100%) from patent arteries were included in the meta-analyses in this review.

Summary

Qualitatively we would expect study validity to be better for the peripheral vascular disease articles than for the carotid artery stenosis studies, because all 20 studies satisfied all the inclusion criteria. In particular, the studies should be in less danger of suffering from verification bias or patient cohort bias. Even so, the 20 articles represent studies on a range of patient populations, and this means that any conclusion drawn by combining their results should be treated cautiously. Patient numbers ranged from 12 to 115 (mean = 34). The number with a stenosis in the relevant range was small in almost all studies (see *Tables 17* to *23*). In all but one article where the sex distribution was reported the majority of patients were male, with the proportion of male patients ranging from 43% to 100% (mean = 71%). One article[138] did not report the sex distribution. The lower limit for patient age ranged from 22 to 56 years (mean = 42 years), and the upper limit ranged from 62 to 97 years (mean = 83 years). Two articles did not report the age range.[82,137] Seven articles gave no information about patient symptoms.[93,95,132,134–137] Eleven articles[93,127,129,130,134–136,138–141] reported how many of the segments included in the analysis were normal, ten did not.[37,82,92,95,128,131–133,136,137] Three articles[93,138,141] excluded normal segments from the analysis; the effect of this is discussed in chapter 8.

As for carotid artery stenosis, follow-up was rare, thus justifying our decision to use a modelling approach to address our questions on the therapeutic impact and effect on the long-term costs and outcomes of MRA and DSA in the diagnosis and management of patients presenting with peripheral vascular disease.

In chapter 6 the results from these articles have been combined using SROC analysis, to give quantitative summary estimates of performance for each MRA technique, where possible, at each of the three dichotomies (0–49% versus 50–100%; 0–49% or 100% versus 50–99%; 0–99% versus 100%). In chapter 7 we assess numerically some of the qualitative observations made above about the effect of the MRA technique, the inclusion of normal segments, and validity. A fuller discussion is given in chapter 8.

TABLE 1 *Number of unique articles retrieved from each database*

	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
Number retrieved	4,649	4,040	3,523	3,732	241	16,185
Number (%) remaining in database after exclusion of duplicates	4,649 (100%)	1,208 (30%)	147 (4%)	1,055 (28%)	124 (51%)	7,183 (44%)

TABLE 2 *Exclusions after application of preliminary electronic exclusion criteria*[*]

	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Total
Review	923	212	38	57	1230
Editorial	42	35	0	46	123
Letter	68	12	1	27	108
Case report	1130	383	23	16	1552
Abstract	0	0	0	473	473
Non-human	259	102	2	37	400
Number excluded	2422	744	64	656	3886
Percentage of unique articles shown in *Table 1* excluded	52%	62%	44%	62%	54%

[*] *The electronic exclusion criteria could not be applied in the Index to Scientific and Technical Proceedings database*

TABLE 3 *Exclusions after application of secondary exclusion criteria*

	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
Review	28	28	7	9	2	74
Letter	4	2	0	0	0	6
Case report	0	0	0	0	0	0
Abstract	1	1	1	0	11	14
Non-human study	1	0	0	0	6	7
Not applicable (not MRA or not carotid or peripheral artery stenosis)	1823	389	66	336	80	2694
Technical	78	16	5	37	23	159
Paediatric study	12	1	0	1	0	14
Ten or fewer patients	105	9	1	8	0	123
Number excluded	2052	446	80	391	122	3091
Percentage of unique articles shown in *Table 1* excluded	44%	37%	54%	37%	98%	43%

TABLE 4 *Numbers of articles remaining after application of secondary exclusion criteria*

	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
Number remaining	175	18	3	8	2	206
Number remaining as percentage of unique articles in *Table 1*	3.8%	1.5%	2.0%	0.8%	1.6%	2.9%

TABLE 5 *Carotid artery stenosis: exclusions after application of final inclusion criteria*

Inclusion criterion		MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
A	No gold standard (conventional angiography)	21	5	1	4	1	32
B	Insufficient data to populate a 2 x 2 table	36	7	0	1	0	44
C	Categories of stenosis not divided at 50%, 70% or 100%	11	1	0	0	0	12
D	Duplicate study group	4	1	0	0	0	5
E	Gold standard method not selective of intra-arterial in all patients, or not stated	13	0	0	0	0	13
F	Calculation of stenosis undefined	4	0	0	0	0	4
G	Study group includes asymptomatic patients	5	0	0	0	0	5
H	Over 1-month time delay between MRA and gold standard examinations	1	0	0	0	0	1
Total number excluded		95	14	1	5	1	116
Percentage of unique articles shown in *Table 1* excluded		2.0%	1.2%	0.7%	0.5%	0.8%	1.6%

TABLE 6 *Carotid artery stenosis: numbers remaining after application of final inclusion criteria*

	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
Numbers remaining	9	0	0	1	0	10
Numbers remaining as percentage of unique articles in *Table 1*	0.2%	0%	0%	0.1%	0%	0.1%

TABLE 7 *Peripheral vascular disease: exclusions after application of final inclusion criteria*

Inclusion criterion	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
A No gold standard (conventional angiography)	12	2	2	0	1	17
B Insufficient data to populate a 2 x 2 table	25	0	0	0	0	25
C Study group not all symptomatic or not specified	6	0	0	0	0	6
D No details of gold standard method given	4	0	0	0	0	4
E Over 1-month or unspecified time delay between MRA and gold standard examinations	4	0	0	0	0	4
F Duplicate study group	2	0	0	0	0	2
Total number excluded	53	2	2	0	1	58
Percentage of unique articles shown in *Table 1* excluded	1.1%	0.2%	1.4%	0%	0.8%	0.8%

TABLE 8 *Peripheral vascular disease: numbers remaining after application of final inclusion criteria*

	MEDLINE	EMBASE	HealthSTAR	Science Citation Index	Index to Scientific and Technical Proceedings	Total
Numbers remaining	18	0	0	2	0	20
Numbers remaining as percentage of unique articles in *Table 1*	0.4%	0%	0%	0.2%	0%	0.3%

TABLE 9 *Number of articles reviewed for resource-use, cost or outcome data*

Paper type	Carotid artery disease	Peripheral vascular disease
Articles identified by search	930	913
Articles screened	96	83
Articles excluded	62	64
Articles met economic inclusion criteria	5	5
Articles excluded on economic criteria	29	14

TABLE 10 *Carotid artery stenosis: contrast-enhanced MRA*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Contrast-enhanced MRA: 0–69% or 100% versus 70–99%													
Scarabino, 1999[96]	A–H	9	0	0	37	1.00	1.00	1.00	1.00	100	–*	0.00	0.20
Remonda, 1998[106]	A–F	17	1	1	25	0.94	0.96	0.94	0.96	95	24.56	0.06	0.41
Martinat, 1998[115]	A–D	10	0	1	43	1.00	0.98	0.91	1.00	98	44.00	0.00	0.19
Sardanelli, 1999[116]	A–D	14	0	0	42	1.00	1.00	1.00	1.00	100	–*	0.00	0.25
Contrast-enhanced MRA: 0–99% versus 100%													
Scarabino, 1999[96]	A–H	3	0	0	43	1.00	1.00	1.00	1.00	100	–*	0.00	0.07
Remonda, 1998[106]	A–F	7	0	0	37	1.00	1.00	1.00	1.00	100	–*	0.00	0.16
Martinat, 1998[115]	A–D	6	0	0	48	1.00	1.00	1.00	1.00	100	–*	0.00	0.11
Sardanelli, 1999[116]	A–D	6	0	0	54	1.00	1.00	1.00	1.00	100	–*	0.00	0.10

FN, number of positive cases incorrectly identified as negative by test; FP, number of negative cases incorrectly identified as positive by test; LR–, likelihood ratio of a negative test result; LR+, likelihood ratio of a positive test result; NPV, negative predictive value; PPV, positive predictive value; TN, number of negative cases correctly identified as negative by test; TP, number of positive cases correctly identified as positive by test

* *Value is undefined owing to division by zero*

TABLE 11 *Carotid artery stenosis: 3D TOF MRA, 0–69% or 100% versus 70–99%*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Fellner, 1997:[117]													
3D FISP	A–D	2	0	6	86	1.00	0.93	0.25	1.00	94	15.33	0.00	0.02
3D TONE†	A–D	2	0	1	91	1.00	0.99	0.67	1.00	99	92.00	0.00	0.02
Link, 1996[94]	A–H	28	3	4	45	0.90	0.92	0.88	0.94	91	11.06	0.11	0.39
Margarelli, 1998[98]	A–H	12	0	0	68	1.00	1.00	1.00	1.00	100	–*	0.00	0.15
Mattle, 1991[118]	A–E	9	1	2	27	0.90	0.93	0.82	0.96	92	13.05	0.11	0.26
Ozaki, 1999[107]	A–F	5	1	15	32	0.83	0.68	0.25	0.97	70	2.61	0.24	0.11
Sardanelli, 1999:[116]													
3D TONE	A–D	14	0	6	34	1.00	0.85	0.70	1.00	89	6.67	0.00	0.26
3D multi-slab†	A–D	14	0	8	34	1.00	0.81	0.64	1.00	86	5.25	0.00	0.25
Scarabino, 1998[99]	A–H	15	0	1	112	1.00	0.99	0.94	1.00	99	113.00	0.00	0.12
Sitzer, 1993[105]	A–G	31	11	8	50	0.74	0.86	0.79	0.82	81	5.35	0.30	0.42

* *Value is undefined owing to division by zero*

† *Duplicated results excluded from meta-analyses*

TABLE 12 *Carotid artery stenosis: 3D TOF MRA, 0–49% or 100% versus 50–99%*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Ozaki, 1999[107]	A–F	11	6	15	21	0.65	0.58	0.42	0.78	60	1.55	0.61	0.32
Uehara, 1995[100]	A–H	13	3	1	64	0.81	0.98	0.93	0.96	95	52.81	0.19	0.20
Wilkerson, 1991[108]	A–E	12	1	1	12	0.92	0.92	0.92	0.92	92	12.00	0.08	0.50

TABLE 13 *Carotid artery stenosis: 3D TOF MRA, 0–99% versus 100%*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Chiesa, 1993[97]	A–H	6	1	4	115	0.86	0.97	0.60	0.99	96	25.5	0.15	0.06
Currie, 1994[111]	A–E	23	0	0	19	1.00	1.00	1.00	1.00	100	–*	0.00	0.55
Fellner, 1997:[117]													
3D FISP†	A–D	3	0	0	91	1.00	1.00	1.00	1.00	100	–*	0.00	0.03
3D TONE		3	0	0	91	1.00	1.00	1.00	1.00	100	–*	0.00	0.03
Link, 1996[94]	A–H	9	0	1	70	1.00	0.99	0.90	1.00	99	71.00	0.00	0.11
Magarelli, 1998[98]	A–H	5	0	0	65	1.00	1.00	1.00	1.00	100	–*	0.00	0.07
Mattle, 1991[118]	A–E	4	0	1	34	1.00	0.97	0.80	1.00	97	35.00	0.00	0.10
Ozaki, 1999[107]	A–F	5	5	1	42	0.50	0.98	0.83	0.89	89	21.50	0.51	0.19
Sardanelli, 1999:[116]													
3D TONE	A–D	6	0	0	54	1.00	1.00	1.00	1.00	100	–*	0.00	0.10
3D multi-slab†	A–D	6	0	0	54	1.00	1.00	1.00	1.00	100	–*	0.00	0.10
Scarabino, 1998[99]	A–H	5	0	0	123	1.00	1.00	1.00	1.00	100	–*	0.00	0.04
Sitzer, 1993[105]	A–G	15	0	2	83	1.00	0.98	0.88	1.00	98	42.50	0.00	0.15
Uehara, 1995[100]	A–H	4	0	3	74	1.00	0.96	0.57	1.00	96	25.67	0.00	0.05
Wilkerson, 1991[108]	A–F	2	0	0	24	1.00	1.00	1.00	1.00	100	–*	0.00	0.08

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 14 *Carotid artery stenosis: 2D TOF MRA, 0–69% or 100% versus 70–99%*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Bianchi, 1995[90]	A–F	8	0	3	10	1.00	0.77	0.72	1.00	86	4.33	0.00	0.38
Dadachanji, 1995[101]	A–H	5	0	0	39	1.00	1.00	1.00	1.00	100	–*	0.00	0.11
Drevet, 1997[109]	A–F	12	0	4	40	1.00	0.91	0.75	1.00	93	11.00	0.00	0.21
Fellner, 1997[117]	A–D	2	0	4	88	1.00	0.96	0.33	1.00	96	23.00	0.00	0.02
Laster, 1993[103]	A–H	41	3	4	151	0.93	0.97	0.91	0.98	96	36.11	0.07	0.22
Nicholas, 1995[122]	A–D	15	2	1	56	0.88	0.98	0.93	0.96	96	50.29	0.12	0.23
Pavone, 1993[124]	A–D	18	1	4	61	0.95	0.94	0.81	0.98	94	15.39	0.06	0.23
Sardanelli, 1999[116]	A–D	14	0	10	32	1.00	0.76	0.58	1.00	82	4.20	0.00	0.25
Scarabino, 1998[99]	A–H	15	0	1	112	1.00	0.99	0.93	1.00	99	113.00	0.00	0.12
Turnipseed, 1993[21]	A–D	29	0	2	23	1.00	0.92	0.93	1.00	96	12.50	0.00	0.54
Young, 1994[23]	A–D	48	8	6	75	0.86	0.93	0.89	0.90	90	11.57	0.15	0.41

* *Value is undefined owing to division by zero*

TABLE 15 *Carotid artery stenosis: 2D TOF MRA, 0–49% or 100% versus 50–99%*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Huston, 1993[102]	A–H	27	0	18	48	1.00	0.73	0.60	1.00	81	3.67	0.00	0.29
Kido, 1991[121]	A–D	18	3	3	35	0.86	0.92	0.86	0.92	90	10.86	0.16	0.36
Litt, 1991:[113]													
observer 1	A–E	57	1	9	25	0.98	0.74	0.86	0.96	89	3.71	0.02	0.63
observer 2*	A–E	52	3	26	13	0.95	0.33	0.67	0.81	69	1.42	0.16	0.59
Nicholas, 1995[122]	A–D	20	5	1	48	0.80	0.98	0.95	0.91	92	39.20	0.20	0.34
Polak, 1992[114]	A–E	22	1	5	13	0.96	0.72	0.81	0.93	85	3.44	0.06	0.56
Riles, 1992[110]	A–F	45	0	12	18	1.00	0.60	0.79	1.00	84	2.50	0.00	0.60

* *Duplicated results excluded from meta-analyses*

TABLE 16 *Carotid artery stenosis: 2D TOF MRA, 0–99% versus 100%*

Study	Inclusion criteria satisfied	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Anson, 1993[112]	A–E	15	0	0	46	1.00	1.00	1.00	1.00	100	–*	0.00	0.25
Bianchi, 1995[90]	A–F	2	0	0	19	1.00	1.00	1.00	1.00	100	–*	0.00	0.10
Buijs, 1993:[119]													
observer 1	A–D	5	0	0	16	1.00	1.00	1.00	1.00	100	–*	0.00	0.24
observer 2†	A–D	5	0	0	16	1.00	1.00	1.00	1.00	100	–*	0.00	0.24
Dadachanji, 1995[101]	A–H	4	0	0	36	1.00	1.00	1.00	1.00	100	–*	0.00	0.10
Drevet, 1997[109]	A–F	3	0	0	53	1.00	1.00	1.00	1.00	100	–*	0.00	0.05
Fellner, 1997[117]	A–D	3	0	0	91	1.00	1.00	1.00	1.00	100	–*	0.00	0.03
Heiserman, 1992:[120]													
observer 1	A–D	8	0	0	65	1.00	1.00	1.00	1.00	100	–*	0.00	0.11
observer 2†	A–D	8	0	0	65	1.00	1.00	1.00	1.00	100	–*	0.00	0.11
observer 3†	A–D	8	0	0	65	1.00	1.00	1.00	1.00	100	–*	0.00	0.11
observer 4†	A–D	8	0	0	65	1.00	1.00	1.00	1.00	100	–*	0.00	0.11
Huston, 1993[102]	A–H	14	0	0	79	1.00	1.00	1.00	1.00	100	–*	0.00	0.15
Kido, 1991[121]	A–D	1	0	1	58	1.00	0.98	0.50	1.00	98	59.00	0.00	0.02
Laster, 1993[103]	A–H	17	0	1	181	1.00	0.99	0.94	1.00	99	182.00	0.00	0.09
Litt, 1991:[113]													
observer 1	A–E	2	5	0	85	0.29	1.00	1.00	0.94	95	–*	0.71	0.08
observer 2†	A–E	2	6	3	83	0.25	0.97	0.40	0.93	90	7.17	0.78	0.09
Nicholas, 1995[122]	A–D	9	0	0	65	1.00	1.00	1.00	1.00	100	–*	0.00	0.12
Pavone, 1992[123]	A–D	2	0	0	52	1.00	1.00	1.00	1.00	100	–*	0.00	0.04
Pavone, 1993[124]	A–D	7	2	1	74	0.78	0.99	0.88	0.97	96	58.33	0.23	0.11
Polak, 1992[114]	A–E	4	0	0	37	1.00	1.00	1.00	1.00	100	–*	0.00	0.10
Riles, 1992[110]	A–F	2	3	0	70	0.40	1.00	1.00	0.96	96	–*	0.60	0.07
Sardanelli, 1999[116]	A–D	6	0	0	54	1.00	1.00	1.00	1.00	100	–*	0.00	0.10
Scarabino, 1998[99]	A–H	5	0	0	123	1.00	1.00	1.00	1.00	100	–*	0.00	0.04
Spartera, 1993[125]	A–D	9	2	1	89	0.82	0.99	0.90	0.98	97	73.64	0.18	0.11
Turnipseed, 1993[21]	A–D	3	0	0	51	1.00	1.00	1.00	1.00	100	–*	0.00	0.06
White, 1994[104]	A–H	12	3	0	120	0.80	1.00	1.00	0.98	98	–*	0.20	0.11
Young, 1994[23]	A–D	12	3	1	121	0.80	0.99	0.92	0.98	97	97.6	0.20	0.11

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 17 *Peripheral vascular disease: contrast-enhanced MRA, 0–49% versus 50–100%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Laissy, 1998[133]	109	3	20	387	0.97	0.95	0.85	0.99	96	19.80	0.03	0.22
Perrier, 1998:[95]												
observer 1	63	5	14	195	0.93	0.93	0.81	0.98	93	13.83	0.08	0.25
observer 2†	64	4	14	194	0.94	0.93	0.82	0.98	93	13.98	0.06	0.25
Quinn, 1997:[135]												
observer 1	31	0	1	86	1.00	0.99	0.97	1.00	99	87.0	0.00	0.36
observer 2†	31	0	0	87	1.00	1.00	1.00	1.00	100	–*	0.00	0.36
Rofsky, 1997[136]	37	1	4	108	0.97	0.96	0.90	0.99	97	27.26	0.03	0.25
Sueyoshi, 1999[139]	67	2	3	351	0.97	0.99	0.96	0.99	99	114.58	0.03	0.16
Winterer, 1999[140]	362	14	43	1361	0.96	0.97	0.89	0.99	97	31.44	0.04	0.21

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 18 *Peripheral vascular disease: contrast-enhanced MRA, 0–49% or 100% versus 50–99%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Perrier, 1998:[95]												
observer 1	17	5	13	242	0.77	0.95	0.57	0.98	94	15.16	0.24	0.08
observer 2†	18	4	15	239	0.82	0.94	0.55	0.98	93	13.85	0.19	0.08
Quinn, 1997:[135]												
observer 1	16	0	1	101	1.00	0.99	0.94	1.00	99	102.00	0.0	0.14
observer 2†	17	0	0	101	1.00	1.00	1.00	1.00	100	–*	0.00	0.14
Sueyoshi, 1999[139]	28	2	2	391	0.93	0.99	0.93	0.99	99	183.40	0.07	0.07
Winterer, 1999[140]	92	16	47	1625	0.85	0.97	0.66	0.99	96	30.30	0.15	0.06

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 19 *Peripheral vascular disease: contrast-enhanced MRA, 0–99% versus 100%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Meaney, 1999:[37]												
observer 1	62	26	4	520	0.70	0.99	0.94	0.95	98	92.3	0.30	0.14
observer 2†	67	2	4	520	0.97	0.99	0.94	1.00	99	127.2	0.03	0.12
Perrier, 1998:[95]												
observer 1	44	2	3	228	0.96	0.99	0.94	0.99	98	73.65	0.04	0.17
observer 2†	44	2	1	229	0.96	1.00	0.98	0.99	99	220.0	0.04	0.17
Quinn, 1997:[135]												
observer 1	15	0	0	103	1.00	1.00	1.00	1.00	100	–*	0.00	0.13
observer 2†	14	0	0	104	1.00	1.00	1.00	1.00	100	–*	0.00	0.12
Sueyoshi, 1999[139]	39	0	1	383	1.00	1.00	0.98	1.00	100	384.0	0.00	0.09
Winterer, 1999[140]	255	13	11	1501	0.95	0.99	0.96	0.99	99	130.79	0.05	0.15

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 20 *Peripheral vascular disease: 2D TOF MRA, 0–49% versus 50–100%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Baumgartner, 1993[93]	24	4	0	13	0.86	1.00	1.00	0.76	90	–*	0.14	0.68
Carpenter, 1994[127]	103	2	2	198	0.98	0.99	0.98	0.99	99	98.10	0.02	0.34
Davis, 1997[129]	82	6	3	45	0.93	0.94	0.96	0.88	98	14.91	0.07	0.65
Ho, 1997[131]	20	8	19	122	0.71	0.87	0.51	0.94	84	5.30	0.33	0.17
Hoch, 1996[82]	172	12	13	155	0.93	0.92	0.93	0.93	93	12.08	0.07	0.52
Laissy, 1995[132]	21	1	1	33	0.95	0.97	0.95	0.97	96	32.45	0.05	0.39
Mulligan, 1991[134]	18	10	30	82	0.64	0.73	0.38	0.89	71	2.40	0.49	0.2
Quinn, 1997:[135]												
observer 1	30	1	3	84	0.97	0.97	0.91	0.99	97	28.06	0.03	0.26
observer 2†	29	2	2	85	0.94	0.98	0.94	0.98	97	40.69	0.07	0.26
Snidow, 1995[137]	80	7	76	215	0.92	0.74	0.51	0.97	78	3.52	0.11	0.23
Yucel, 1993[141]	65	6	16	119	0.92	0.88	0.80	0.95	89	7.72	0.10	0.34

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 21 *Peripheral vascular disease: 2D TOF MRA, 0–49% or 100% versus 50–99%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Baumgartner, 1993[93]	18	5	0	18	0.78	1.00	0.10	0.78	88	–*	0.22	0.56
Carpenter, 1994[127]	33	1	2	269	0.97	0.99	0.94	1.00	99	131.51	0.03	0.11
Davis, 1997[129]	44	10	16	84	0.81	0.84	0.73	0.89	83	5.09	0.22	0.35
Ho, 1997[131]	13	9	18	129	0.59	0.88	0.42	0.93	84	4.83	0.47	0.13
Hoch, 1996[82]	59	13	21	259	0.82	0.93	0.74	0.95	90	10.93	0.20	0.20
Mulligan, 1991[134]	6	7	25	102	0.46	0.80	0.19	0.94	77	2.34	0.67	0.09
Quinn, 1997:[135]												
observer 1	13	3	3	99	0.81	0.97	0.81	0.97	95	27.63	0.19	0.14
observer 2†	14	3	2	99	0.82	0.98	0.88	0.97	96	41.59	0.18	0.14
Yucel, 1993[141]	21	10	16	159	0.68	0.91	0.57	0.94	87	7.41	0.36	0.15

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 22 *Peripheral vascular disease: 2D TOF MRA, 0–99% versus 100%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Baumgartner, 1993[93]	5	0	1	35	1.00	0.97	0.83	1.00	98	36.00	0.00	0.12
Carpenter, 1994[127]	69	2	1	233	0.97	1.00	0.99	0.99	99	227.41	0.03	0.23
Davis, 1997[129]	38	14	5	97	0.73	0.95	0.88	0.87	88	14.91	0.28	0.34
Eklof, 1998[130]	59	10	18	52	0.86	0.74	0.77	0.84	80	3.33	0.20	0.50
Ho, 1997[131]	4	2	4	159	0.67	0.98	0.50	0.99	96	27.17	0.34	0.04
Hoch, 1996[82]	101	11	4	236	0.90	0.98	0.96	0.96	96	54.11	0.10	0.32
Mulligan, 1991[134]	10	5	7	118	0.67	0.94	0.59	0.96	91	11.90	0.35	0.11
Quinn, 1997:[135]												
observer 1	15	0	2	101	1.00	0.98	0.88	1.00	98	51.50	0.00	0.13
observer 2†	14	0	1	103	1.00	0.99	0.93	1.00	99	104.00	0.00	0.12
Timonina, 1999[92]	36	1	0	183	0.97	1.00	1.00	0.99	100	–*	0.03	0.17
Yucel, 1993[141]	40	0	4	162	1.00	0.98	0.91	1.00	98	41.50	0.00	0.19

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

TABLE 23 *Peripheral vascular disease: results for vessels above the knee and below the knee, any MRA technique, 0–49% versus 50–100%*

Study	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR–	Prevalence
Above knee												
Baumgartner, 1993[93]	24	4	0	13	0.86	1.00	1.00	0.76	90	–*	0.14	0.68
Carpenter, 1994[127]	103	2	2	198	0.98	0.99	0.98	0.99	99	98.10	0.02	0.34
Ho, 1997[131]	20	8	19	122	0.71	0.87	0.51	0.94	84	5.30	0.33	0.17
Laissy, 1995[132]	21	1	1	33	0.95	0.97	0.95	0.97	96	32.45	0.05	0.39
Perrier, 1998[95]	63	5	14	195	0.93	0.93	0.82	0.98	93	13.83	0.08	0.25
Quinn, 1997:[135]												
observer 1, contrast enhanced	31	0	1	86	1.00	0.99	0.97	1.00	99	87.00	0.00	0.26
observer 2,† contrast enhanced	31	0	0	87	1.00	1.00	1.00	1.00	100	–*	0.00	0.26
observer 1, 2D	30	1	3	84	0.97	0.97	0.91	0.99	97	28.06	0.03	0.26
observer 2,† 2D	29	2	2	85	0.94	0.98	0.94	0.98	97	40.69	0.07	0.26
Snidow, 1995[137]	51	5	65	120	0.91	0.65	0.44	0.96	71	2.59	0.14	0.23
Sueyoshi, 1999[139]	35	0	3	149	1.00	0.98	0.92	1.00	98	50.67	0.00	0.19
Winterer, 1999[140]	189	0	21	879	1.00	0.98	0.90	1.00	98	42.86	0.00	0.17
Yucel, 1993[141]	25	2	11	55	0.93	0.83	0.69	0.96	86	5.56	0.09	0.29
Below knee												
Cortell, 1996[128]	172	3	10	208	0.98	0.95	0.95	0.99	97	21.43	0.02	0.45
Davis, 1997[129]	82	6	3	45	0.93	0.94	0.96	0.88	93	14.91	0.07	0.65
Eklof, 1998[130]	59	14	2	31	0.81	0.94	0.97	0.69	85	13.34	0.20	0.69
Laissy, 1998[133]	47	2	11	220	0.96	0.95	0.81	0.99	95	20.14	0.04	0.18
Snidow, 1995[137]	29	2	11	95	0.94	0.90	0.73	0.98	91	9.01	0.07	0.23
Sueyoshi, 1999[139]	30	2	0	200	0.94	1.00	1.00	0.99	99	–*	0.06	0.14
Winterer, 1999[140]	130	13	7	541	0.91	0.99	0.95	0.98	97	71.17	0.09	0.21
Yucel, 1993[141]	36	3	3	40	0.92	0.93	0.92	0.93	93	13.23	0.08	0.48

* *Value is undefined owing to division by zero*
† *Duplicated results excluded from meta-analyses*

Chapter 5

Details of studies excluded from the review

The reasons for the exclusion of 96 articles on carotid artery stenosis that were not excluded using the preliminary and secondary exclusion criteria, but did not satisfy the inclusion criteria A–D, are given in alphabetical order in *Table 24*. Thirty-two articles[20,142–172] were excluded because they did not use the gold standard of DSA or cut-film angiography; 47 articles[7,87,88,164,173–214,322] were excluded because they did not report enough data to allow completion of a 2 × 2 contingency table; 12 articles[215–226] did not report performance at 50%, 70% or 100% stenosis; and five articles[227–231] had the same group of participants as another article.

The reasons for the exclusion of 59 articles on peripheral vascular disease that were not excluded using the preliminary and secondary exclusion criteria, but did not satisfy the final inclusion criteria, are given in alphabetical order in *Table 25*. Seventeen articles[232–248] were excluded because they did not use the gold standard of DSA or cut-film angiography; 25 articles[249–273] were excluded because they did not report enough data to allow completion of a 2 × 2 contingency table; six studies[274–279] included asymptomatic participants; five articles[89,216,280–282] did not describe the gold standard technique; four articles[83,283–285] did not specify a period of less than 1 month between tests; and two studies[286,287] had the same group of participants as another article.

Each article may have failed to satisfy more than one of the inclusion criteria. The reason for exclusion given above is the first criterion that the article failed to satisfy. Other reasons are shown in *Tables 24* and *25*.

TABLE 24 *The 96 excluded carotid artery stenosis articles*

Study	Exclusion criterion			
	A: No gold standard	**B: Insufficient data to populate a 2 x 2 table**	**C: Categories of stenosis not divided at 50%, 70% or 100%**	**D: Duplicate study group**
Anderson, 1992[227]	No	No	No	Yes
Anderson, 1994[173]	No	Yes	No	No
Applegate, 1992[174]	No	Yes	Yes	No
Ascer, 1996[175]	No	Yes	No	No
Auffray-Calvier, 1996[228]	No	No	No	Yes
Blatter, 1993[176]	No	Yes	No	No
Carriero, 1990[142]	Yes	Yes	Yes	No
Carriero, 1991[177]	No	Yes	No	No
Carriero, 1993[215]	No	No	Yes	No
Carriero, 1995[216]	No	No	Yes	No
Carriero, 1998[178]	No	Yes	No	No
Chen, 1994[179]	No	Yes	Yes	No
Cotilla, 1998[217]	No	No	Yes	No
De Marco, 1994[180]	No	Yes	Yes	No
Edelman, 1990[181]	No	Yes	No	No
Enochs, 1998[143]	Yes	Yes	Yes	No
Erdoes, 1996[182]	No	Yes	No	No
Felber, 1990[144]	Yes	Yes	No	No
Freeman, 1993[183]	No	Yes	No	No
Friedrich, 1993[184]	No	Yes	No	No
Furst, 1993[185]	No	Yes	No	No
Furst, 1999[218]	No	No	Yes	No
Furuya, 1992[186]	No	Yes	Yes	No
Goldman, 1999[145]	Yes	Yes	No	No
Gortler, 1994[146]	Yes	Yes	Yes	No
Hartmann, 1999[187]	No	Yes	Yes	No
Heiserman, 1996[219]	No	No	Yes	No
Heros, 1994[147]	Yes	Yes	Yes	No
Horn, 1994[148]	Yes	Yes	Yes	No
Huang, 1995[188]	No	Yes	Yes	No
Huston, 1998[189]	No	Yes	No	No
Huston, 1999[149]	Yes	Yes	Yes	No
Ishikawa, 1999[88]	No	Yes	–	–
Isoda, 1998[150]	Yes	Yes	Yes	No
Jackson, 1998[220]	No	No	Yes	No
Kido, 1991[229]	No	No	No	Yes
Kramer, 1990[230]	No	No	No	Yes
Kramer, 1993[221]	No	No	Yes	No
Kuntz, 1995[322]	No	Yes	Yes	No
Leclerc, 1998[190]	No	Yes	Yes	No
Leclerc, 1999[151]	Yes	Yes	Yes	No
Lee, 1999[152]	Yes	Yes	Yes	No
Levi, 1996[191]	No	Yes	No	No
Levine, 1994[192]	No	Yes	Yes	No
Li, 1992[153]	Yes	Yes	No	No

continued

TABLE 24 contd *The 96 excluded carotid artery stenosis articles*

Study	Exclusion criterion			
	A: No gold standard	**B: Insufficient data to populate a 2 x 2 table**	**C: Categories of stenosis not divided at 50%, 70% or 100%**	**D: Duplicate study group**
Liberopoulos, 1996[222]	No	No	Yes	No
Liu, 1996[154]	Yes	Yes	No	No
Lui, 1996[87]	No	Yes	–	–
Lustgarten, 1994[155]	Yes	Yes	No	No
Masaryk, 1990[156]	Yes	Yes	Yes	No
Masaryk, 1991[193]	No	Yes	Yes	No
Mayberg, 1994[157]	Yes	Yes	Yes	No
Meder, 1993[194]	No	Yes	Yes	No
Melhem, 1998[158]	Yes	Yes	No	No
Mittl, 1994[195]	No	Yes	No	No
Modaresi, 1999[196]	No	Yes	Yes	No
Mukherjee, 1998[197]	No	Yes	Yes	No
Muto, 1996[159]	Yes	Yes	No	No
Noldeke, 1992[160]	Yes	Yes	No	No
Obuchi, 1999[161]	Yes	Yes	Yes	No
Pan, 1992[198]	No	Yes	Yes	No
Pan, 1995[162]	Yes	Yes	Yes	No
Patel, 1995[199]	No	Yes	No	No
Peng, 1996[200]	No	Yes	No	No
Peters, 1990[223]	No	No	Yes	No
Polak, 1993[20]	Yes	Yes	No	No
Provinciali, 1992[201]	No	Yes	Yes	No
Rasanen, 1999[202]	No	Yes	Yes	No
Saloner, 1996[203]	No	Yes	Yes	No
Saouaf, 1998[163]	Yes	Yes	No	No
Sameshima, 1999[204]	No	Yes	No	No
Scarabino, 1997[205]	No	Yes	No	No
Sinitsyn, 1995[206]	No	Yes	Yes	No
Slosman, 1998[207]	No	Yes	Yes	No
Smith, 1994[164]	No	Yes	Yes	No
Strotzer, 1998[224]	No	No	Yes	No
Suzuki, 1995[165]	Yes	Yes	Yes	No
Tamiya, 1996[166]	Yes	Yes	No	No
Toh, 1993[225]	No	No	Yes	No
Turnipseed, 1993[231]	No	No	No	Yes
Ueda, 1997[167]	Yes	Yes	Yes	No
Uehara, 1996[168]	Yes	Yes	No	No
Uehara, 1997[169]	Yes	Yes	Yes	No
van Everdingen, 1997[208]	No	Yes	No	No
van Everdingen, 1998[209]	No	Yes	No	No
van der Grond, 1996[170]	Yes	Yes	Yes	No
Vanninen, 1995[171]	Yes	Yes	No	No
Vanninen, 1995[211]	No	Yes	No	No
Vanninen, 1996[210]	No	Yes	No	No
Villa, 1991[212]	No	Yes	Yes	No
Vogl, 1995[226]	No	No	Yes	No
Willig, 1998[172]	Yes	Yes	No	No
Yokogami, 1998[213]	No	Yes	No	No
Young, 1996[214]	No	Yes	No	No

TABLE 25 *The 59 excluded peripheral vascular disease articles*

Study	Exclusion criterion					
	A: No gold standard	**B: Insufficient data to populate a 2 x 2 table**	**C: Not all symptomatic**	**D: Problems with gold standard**	**E: Over 1 month or unspecified time between tests**	**F: Duplicate study group**
Adamis, 1995[274]	No	No	Yes	No	No	No
Amano, 1997[232]	Yes	Yes	Not known	Not known	Not known	Not known
Baum, 1995[249]	No	Yes	No	No	Yes	No
Bendib, 1997[250]	No	Yes	Yes	No	No	No
Boos, 1995[251]	No	Yes	No	Yes	Yes	No
Busch, 1999[252]	No	Yes	Yes	No	No	No
Cambria, 1993[283]	No	No	No	No	Yes	No
Cambria, 1997[253]	No	Yes	No	No	Yes	No
Carpenter, 1992[286]	No	No	No	No	No	Yes
Carpenter, 1994[233]	Yes	Yes	No	Yes	Yes	No
Carpenter, 1996[254]	No	Yes	No	No	Yes	No
Carriero, 1998[323]	No	No	No	Yes	No	No
Currie, 1995[234]	Yes	Yes	No	Yes	Yes	No
Dobkowski, 1998[255]	No	Yes	Yes	Yes	Yes	No
Earls, 1998[235]	Yes	Yes	Yes	Yes	Yes	No
Forster, 1999[236]	Yes	Yes	No	Yes	Yes	No
Gibbs, 1994[237]	Yes	Yes	Yes	Yes	Yes	No
Glickerman, 1996[284]	No	No	No	No	Yes	No
Hany, 1998[238]	Yes	Yes	No	Yes	Yes	No
Hertz, 1993[256]	No	Yes	No	Yes	Yes	No
Hertz, 1994[239]	Yes	Yes	Yes	Yes	Yes	No
Ho, 1998[240]	Yes	Yes	No	Yes	Yes	No
Ho, 1998[257]	No	Yes	Yes	No	No	No
Hoch, 1999[83]	No	No	No	No	Yes	No
Huber, 1997[258]	No	Yes	No	No	Yes	No
Jones, 1998[259]	No	Yes	No	No	Yes	No
Krug, 1995[280]	No	No	No	Yes	Yes	Yes
Krug, 1995[281]	No	No	No	Yes	Yes	Yes
Lee, 1998[241]	Yes	Yes	Yes	Yes	Yes	No
Levy, 1998[242]	Yes	Yes	Yes	Yes	Yes	No
Leyendecker, 1997[260]	No	Yes	No	No	No	No
Leyendecker, 1998[261]	No	Yes	No	No	No	No
Link, 1999[275]	No	No	Yes	No	No	No
McCauley, 1994[262]	No	Yes	Yes	No	No	No
Maeda, 1996[89]	No	No	No	Yes	Yes	No
Mohiaddin, 1991[243]	Yes	Yes	Yes	Yes	Yes	No
Owen, 1993[287]	No	No	No	No	No	Yes
Poon, 1997[276]	No	No	Yes	No	Yes	No
Quinn, 1993[263]	No	Yes	Yes	No	No	No
Quinn, 1998[264]	No	Yes	No	No	No	No
Reimer, 1997[244]	Yes	Yes	Yes	Yes	Yes	No
Reimer, 1998[265]	No	Yes	No	Yes	Yes	No
Reimer, 1999[266]	No	Yes	Yes	Yes	Yes	No

continued

TABLE 25 contd *The 59 excluded peripheral vascular disease articles*

Study	Exclusion criterion					
	A: No gold standard	**B: Insufficient data to populate a 2 x 2 table**	**C: Not all symptomatic**	**D: Problems with gold standard**	**E: Over 1 month or unspecified time between tests**	**F: Duplicate study group**
Sarkar, 1998[245]	Yes	Yes	No	Yes	Yes	No
Schnapf, 1992[246]	Yes	Yes	Yes	Yes	Yes	No
Sivananthan, 1993[282]	No	No	No	Yes	No	No
Snidow, 1995[267]	No	Yes	Yes	No	No	No
Snidow, 1996[285]	No	No	No	No	Yes	No
Steffens, 1999[268]	No	Yes	No	No	No	No
Swan, 1996[277]	No	No	Yes	Yes	Yes	No
Swan, 1997[269]	No	Yes	No	No	Yes	No
Vosshenrich, 1993[270]	No	Yes	Yes	Yes	Yes	Yes
Vosshenrich, 1996[278]	No	No	Yes	Yes	Yes	Yes
Vosshenrich, 1998[247]	Yes	Yes	No	Yes	Yes	No
Vosshenrich, 1998[248]	Yes	Yes	No	Yes	Yes	No
Winchester, 1998[279]	No	No	Yes	No	No	No
Yamashita, 1997[271]	No	Yes	Yes	Yes	Yes	No
Yamashita, 1998[272]	No	Yes	Yes	Yes	Yes	No
Yoshikawa, 1994[273]	No	Yes	Yes	Yes	Yes	No

Chapter 6

Results of the review

The results of the review are presented in this chapter, organised by research question.

Carotid artery disease

Compared with the gold standard of intra-arterial X-ray DSA, what is the diagnostic accuracy of contrast-enhanced MRA techniques in determining stenosis of the internal carotid artery?

Only four articles using contrast-enhanced MRA techniques were included in the review,[96,106,115,116] so no meta-analysis was performed. The articles reported results only for the 0–69% or 100% versus 70–99% and 0–99% versus 100% levels. Results (see *Table 10*) were better than those from the earlier MRA techniques, especially with regard to specificity. The results are not shown plotted on a graph as they are all very similar.

Compared with the gold standard of intra-arterial X-ray DSA, what is the diagnostic accuracy of 3D TOF MRA techniques in determining stenosis of the internal carotid artery?

0–69% or 100% versus 70–99%

Results from seven articles[94,98,99,105,107,116,117] were included in the meta-analysis. The SROC curve (*Figure 7*) has $Q^* = 0.98$ (95% CI, 0.93 to 1.00).

0–49% or 100% versus 50–99%

Results were available from only three articles,[100,107,108] so no meta-analysis was performed. The results are shown in *Table 12* and *Figure 8*.

0–99% versus 100%

Results from 11 articles[94,97–100,105,107,108,111,116,117] were included in the meta-analysis. The SROC curve (*Figure 9*) has $Q^* = 0.997$ (95% CI, 0.992 to 1.00).

Compared with the gold standard of intra-arterial X-ray DSA, what is the diagnostic accuracy of 2D TOF MRA techniques in determining stenosis of the internal carotid artery?

0–69% or 100% versus 70–99%

Results from ten articles[21,90,99,101,103,109,116,117,122,124] were included in the meta-analysis. The SROC curve (*Figure 10*) has $Q^* = 0.99$ (95% CI, 0.97 to 1.00).

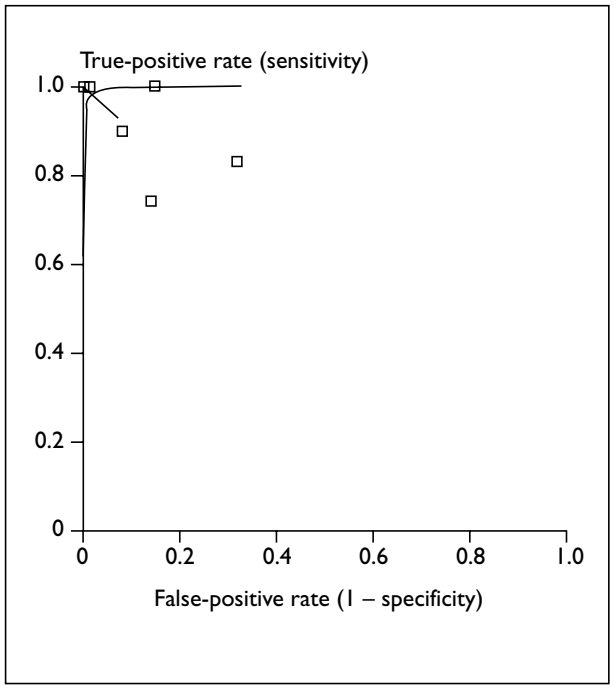

FIGURE 7 *Carotid artery disease: SROC curve for 3D TOF MRA, 0–69% or 100% versus 70–99% (number of studies included = 7). The straight line shows the 95% CI for Q^*; two points coincide at (0.01, 1)*

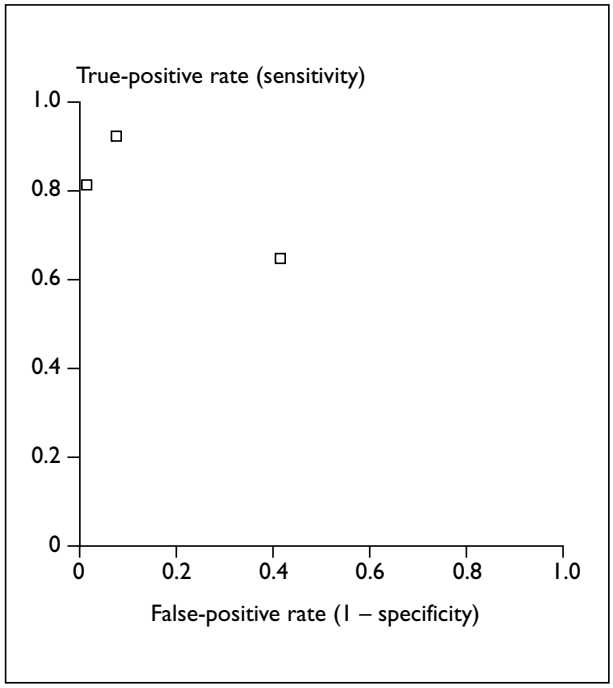

FIGURE 8 *Carotid artery disease: results for 3D TOF MRA, 0–49% or 100% versus 50–99% (number of studies included = 3)*

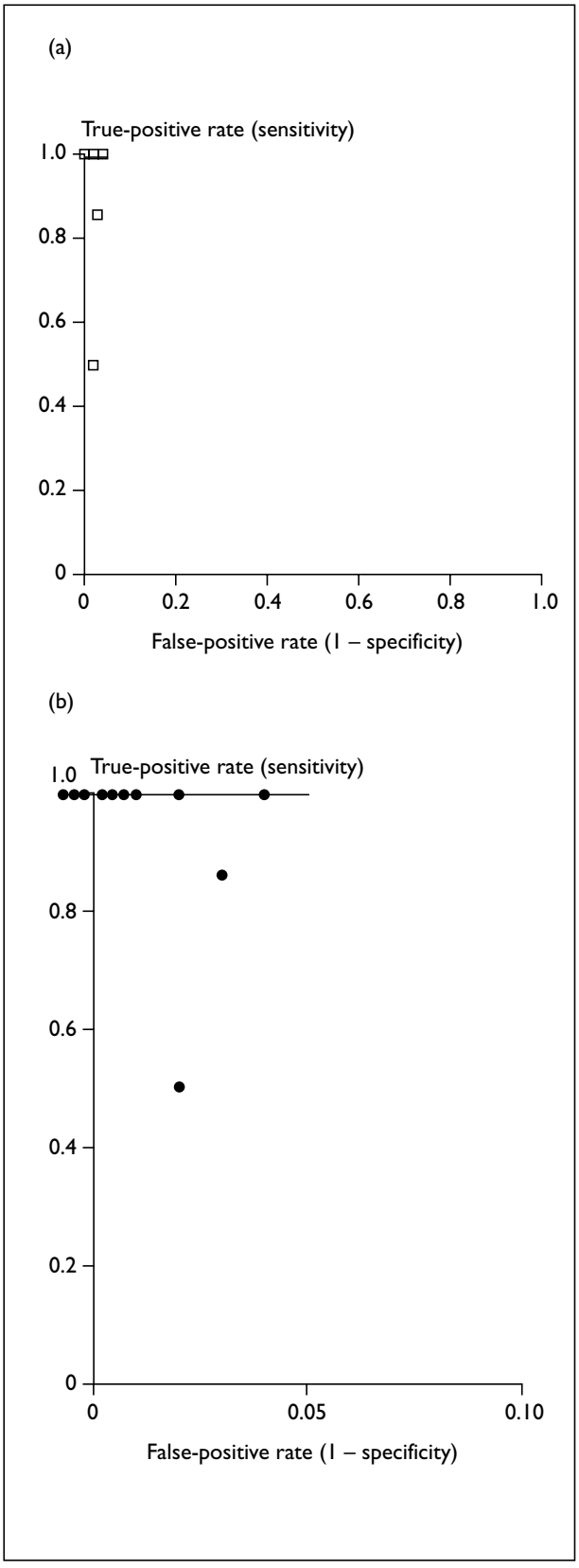

FIGURE 9 *Carotid artery disease. (a) SROC curve for 3D TOF MRA, 0–99% versus 100% (number of studies included = 11). The straight line shows the 95% CI for Q*. (b) Expansion of region with a false-positive rate < 0.1, with points plotted offset from one another when overlapping*

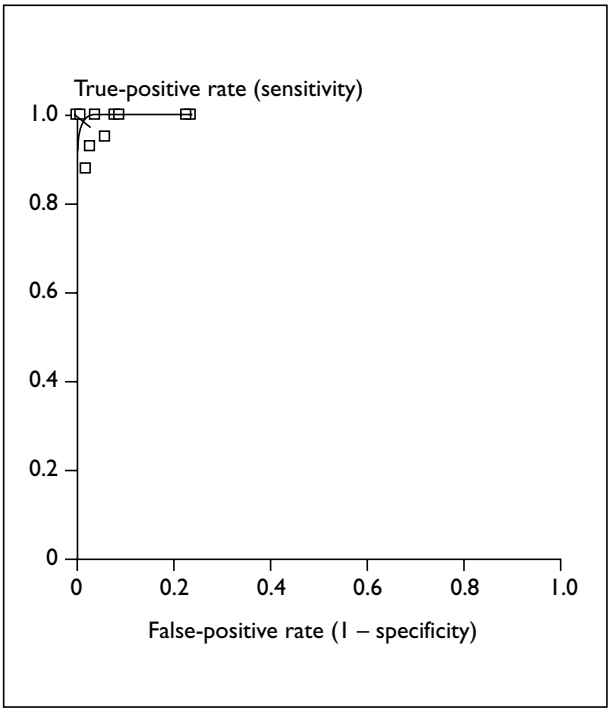

FIGURE 10 *Carotid artery disease: SROC curve for 2D TOF MRA, 0–69% or 100% versus 70–99% (number of studies included = 10). The straight line shows the 95% CI for Q*; there are no overlapping points*

0–49% or 100% versus 50–99%

Results from six articles[102,110,113,114,121,122] were included in the meta-analysis. The SROC curve (*Figure 11*) has $Q^* = 0.92$ (95% CI, 0.84 to 1.00).

0–99% versus 100%

Results from 21 articles[21,90,99,101–104,109,110,112–114,116,117,119–125] were included in the meta-analysis. The SROC curve (*Figure 12*) has $Q^* = 1.00$ (95% CI, 0.998 to 1.00).

Compared with the gold standard of intra-arterial X-ray DSA, what is the diagnostic accuracy of phase-contrast MRA techniques, in determining stenosis of the internal carotid artery?

Only two[21,99] of the articles included in the review used phase-contrast techniques. In the latter study,[99] no results for phase-contrast alone were presented. Scarabino and co-workers[99] found that the 3D phase-contrast technique, for the 0–69% or 100% versus 70–99% dichotomy, had a sensitivity of 93% and a specificity of 98%. This compares with 100% and 99% using 3D TOF, in the same article.

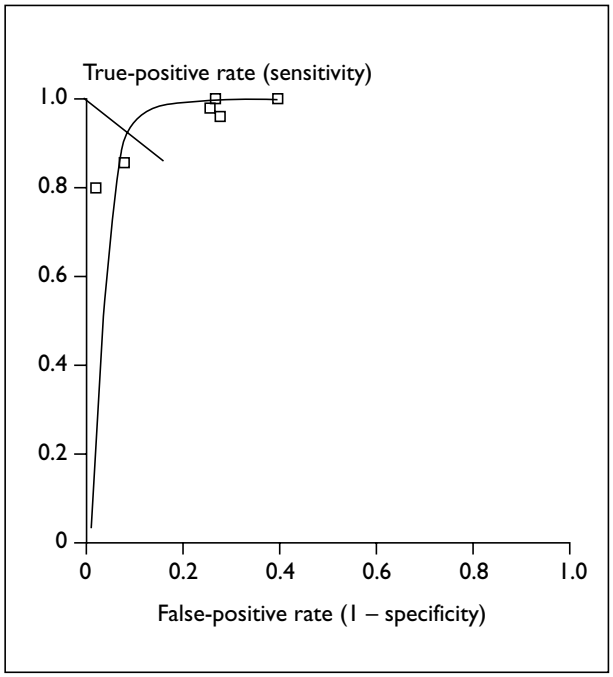

FIGURE 11 *Carotid artery disease: SROC curve for 2D TOF MRA, 0–49% or 100% versus 50–99% (number of studies included = 6). The straight line shows the 95% CI for Q*; there are no overlapping points*

Compared with the gold standard of intra-arterial X-ray DSA, what is the diagnostic accuracy of the TOF and phase-contrast MRA techniques in identifying tandem lesions in carotid artery disease?

There are few data available to answer this question. Nine[98,99,101,103,107,114,118,121,122] of the articles included in the review did not mention tandem lesions at all. Sixteen articles raised the issue, but did not present any data from their own study.[21,23,96,97,100,104,105,109–113,119,120,123,125] Early work by Huston and co-workers[102] used 2D TOF with a limited field of view, and the authors noted that they did not detect lesions "including intracranial tandem lesions and substantial stenosis at carotid and vertebral artery origins".

In those articles that addressed the question, only one[31] measured a percentage stenosis for intracranial vessels. Because this article investigated only intracranial vessels it was not included in the diagnostic performance part of the review, but it satisfied inclusion criteria A–F (see *Table 41*). The authors found that experienced observers were aware of artefacts that can give the appearance of greater stenosis, and overcompensated for the problem, resulting in underestimation of the lesion. Of the 50–99% intracranial internal carotid artery stenoses, 74% were underestimated with MRA.

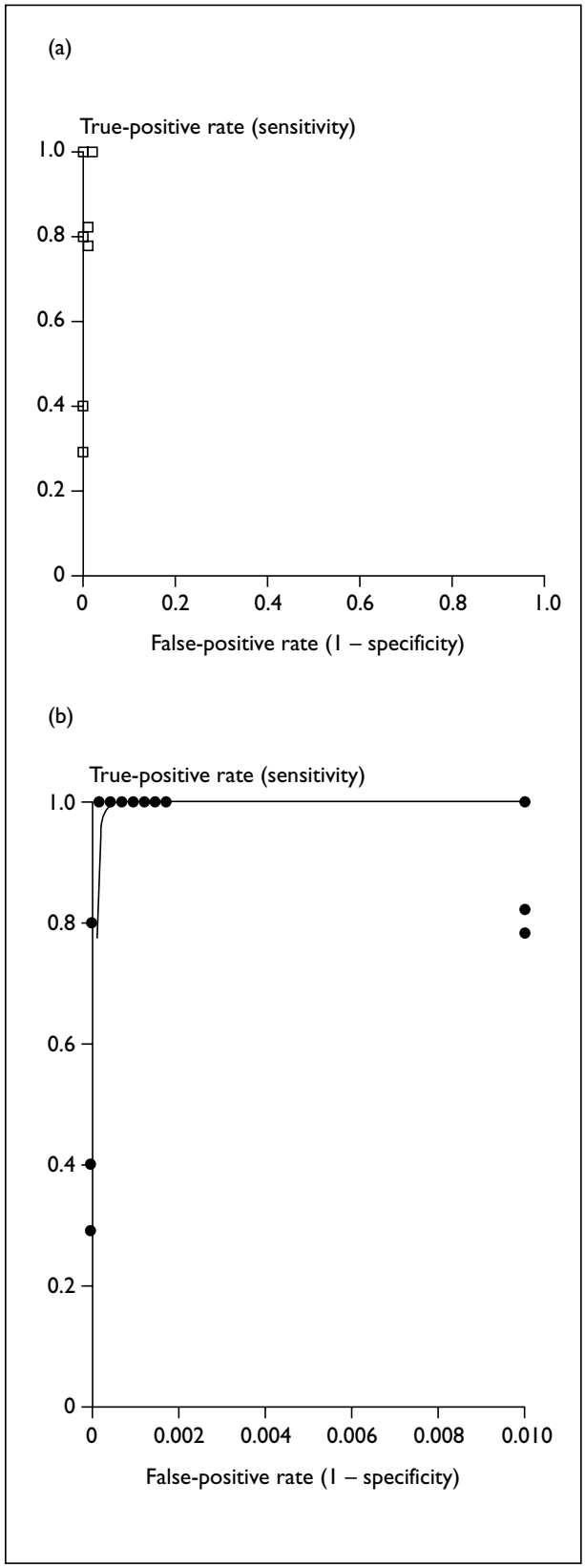

FIGURE 12 *Carotid artery disease: SROC curve for 2D TOF MRA, 0–99% versus 100%. (a) The curve is coincident with the true-positive rate axis and cannot be seen (number of studies included = 21). (b) Expansion of the region with a false-positive rate < 0.01, with points plotted offset from one another when overlapping in the false-positive rate. There are 14 points at (0, 1)*

In the other articles the aim was not to measure the degree of stenosis, as was done for the internal carotid artery, but usually to grade the images on their potential for being diagnostic. The reasons for this approach are two-fold. Firstly, it is known that images obtained of the region are often poor, and it is not possible to make measurements. Thus a first step in the assessment of MRA is simply to determine whether or not images are of diagnostic quality. Secondly, intracranial lesions are uncommon and occur only once in every 50 cases. By considering the potential for diagnosis, images from all the patients in a study may be assessed, and not just the images from the limited number of patients where there is a lesion present. The most systematic investigation was done by Fellner and co-workers.[117] They used a head and neck coil to facilitate imaging of the supra-aortic arteries, and classified images by anatomic region as assessment possible, assess-ment uncertain or assessment impossible. For coronal 3D FISP images the proportions were 89%, 10% and 1%, while for axial 3D TOF 98% of images could be assessed and in 2% assessment was uncertain. These results are similar to those reported by Martinat and co-workers[115] who, although noting that analysis in the carotid siphon and circle of Willis was more difficult, reported that 3D FISP allowed evaluation in 90% of cases. Sardanelli and co-workers[116] obtained less impressive results using contrast-enhanced MRA (3D FISP). Out of 30 cases the origin of the supra-aortic vessels was visualised with sufficient diagnostic information in only eight (27%), these being patients with short necks. Wilkerson and co-workers[108] noted that intrathoracic and carotid siphon disease was not evaluable by 3D maximum intensity projection (MIP) from 2D TOF MRA, because disease was missed, although this conclusion was not justified by analysis of the proportion of patients in which assessment was unsatisfactory. Remonda and co-workers[106] used a large field of view from the aortic arch to the circle of Willis. In one case (of 44 vessels) another significant stenosis was detected by both MRA and DSA, but there was no comment about the diagnostic potential of images in cases where no lesion was present. Bianchi and co-workers[90] noted the technical problems involved with imaging the siphon, and simply sought the presence or absence of morphological symmetry at the carotid siphon in nine patients. Although asymmetry was seen in two cases using MRA, there were no tandem lesions at the siphon seen with DSA.

What is the diagnostic impact of the MRA methodologies in comparison with duplex ultrasound?

Fourteen articles[21,23,102,104,105,108–111,114,118,119,122,125] were included in the review that examined the diagnostic performance of ultrasound as well as that of MRA. In one of these articles[125] the ultrasound performance was compared directly to MRA, but in the other studies both MRA and ultrasound were compared with conventional angiography for the same group of patients. Two articles[23,118] quoted a composite MRA result for more than one imaging sequence. Mattle and co-workers[118] found that ultrasound had a lower sensitivity and specificity than MRA for diagnosis of 70–99% versus 0–69% or 100% stenosis, but was better in the diagnosis of complete occlusion. In contrast, Young and co-workers[23] found higher sensitivity for ultrasound for the diagnosis of both 70–99% versus 0–69% or 100% dichotomy and the 100% versus 0–99% dichotomy. However, the specificity of the two techniques was the same. Three articles assessed the use of 3D TOF.[105,108,111] Ultrasound performed slightly less well in diagnosing complete occlusion in one study[111] and slightly better in another.[105] The sensitivity at the 50–99% versus 0–49% or 100% level was equally good for 3D TOF MRA and ultrasound, but the specificity was lower for ultrasound.[108] At the 70–99% versus 0–69% or 100% level, both sensitivity and specificity were better for ultrasound.[105] Of these three studies, the one by Sitzer and co-workers[105] involved the largest study group and satisfied more of the inclusion criteria than the other articles.

Two articles[21,109] compared 2D TOF with ultrasound for the diagnosis 70–99% versus 0–69% or 100% stenosis. Both articles reported 100% sensitivity for 2D TOF MRA, which equalled the sensitivity for ultrasound in one article[109] and was better than the sensitivity for ultrasound in the other. The specificity of 2D TOF MRA was found to be higher than that of ultrasound by Drevet and co-workers[109] and to be equal to that of ultrasound by Turnipseed and co-workers.[21] Eight studies[21,102,104,109,110,114,119,122] compared 2D TOF with ultrasound for the diagnosis of complete occlusion. All eight of these articles reported 100% specificity for both 2D TOF and ultrasound for the diagnosis of complete occlusion. The sensitivity results are illustrated in *Figure 13*. Only one article reported a lower sensitivity for MRA than for ultrasound.[110]

What are the long-term costs and outcomes of MRA and DSA in the diagnosis and management of people presenting with carotid arterial disease?

Probability of events

The data on sensitivity and specificity of MRA to detect 70–99% stenosis were derived from the ten articles[94,96–104] that met the inclusion criteria A–H for the clinical systematic review. The data for all

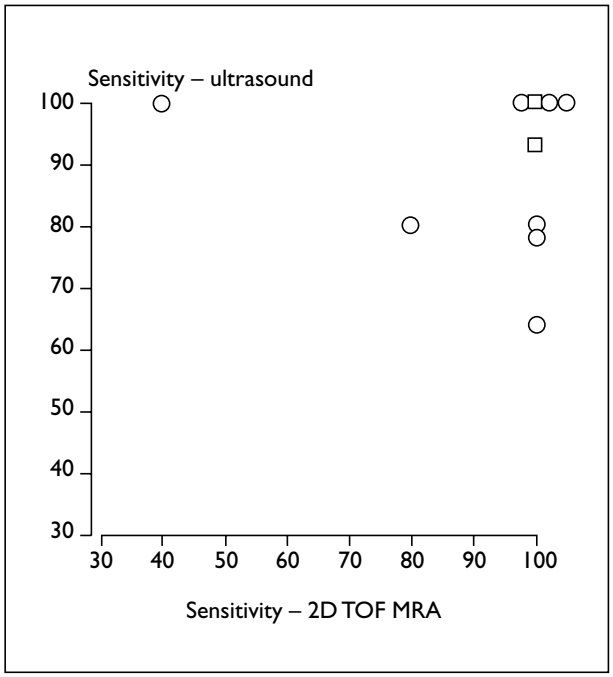

FIGURE 13 *Carotid artery disease: comparison of sensitivity of 2D TOF MRA and ultrasound for the diagnosis of complete occlusion*[21,102,104,109,110,114,119,122] *or of 70–99% versus 0–69% or 100% stenosis.* [21,109] *The four points at (100, 100) have been plotted offset from one another for clarity (○, Complete occulsion; □, 70–99% versus 0–69% or 100% stenosis)*

MRA techniques were combined. This approach was taken to increase the generalisability of the analysis to different settings, because the results of the survey indicated that a range of MRA techniques is available and used in the UK. The results for MRA showed a high level of sensitivity (93%) and specificity (overall 94%). The probabilities of positive or negative MRA tests were also estimated from these ten articles. In the sensitivity analysis, higher levels of sensitivity (overall 95%) and specificity (overall 98%) were used. These were derived from the articles that only met inclusion criteria A–D.[21,23,115–125]

The probability of endarterectomy following DSA was estimated as the prevalence of 70–99% stenosis in the trial population (21%). The probability of endarterectomy following MRA was estimated as the proportion of patients diagnosed with this degree of stenosis by MRA (25%).

The probability that combined evaluation with MRA and ultrasound is concordant (82–84%) was estimated from the studies included in the systematic review[21,23,102,104,105,108–111,114,118,119,122,125] and one study that was not included[199] (insufficient data to complete a 2 × 2 table). The sensitivity (94–100%) and specificity (91–92%) were estimated from the same sources.

The probability of stroke as a result of DSA was estimated (overall 1.8%) from three articles.[107,199,288] This estimate is lower than that previously indicated in chapter 1.[4–7] However, it has the advantage of being derived from comparative evaluations of DSA and MRA. The data from these sources were combined with the data from the NASCET and ECST trials to estimate the probability of non-disabling stroke (46%), disabling stroke (34%) and death (20%) for people who had a stroke incident related to DSA.[8,9]

Most of the probability data for events following surgery or medical management for carotid artery disease were derived from the results of the NASCET and ECST trials.[8,9] Exceptions are described below. The randomised controlled design of these trials and the large sample size suggest the data are internally valid for the trial settings and population. However, the investigators acknowledge that the benefits of endarterectomy may be lower when used outside the trial setting and population.[8,9] This may bias the analysis. The direction of bias is likely to favour tests with higher sensitivity that accurately predict patients eligible for the procedure. In the sensitivity analysis the possibility of a lower level of benefit from endarterectomy was simulated by increasing the probability of disabling stroke and death associated with endarterectomy at 5 years to be equivalent to those of medical management.

The trials[8,9] were used as the source of all the data required to estimate the probability of events following surgery or medical management, excluding the complications associated with the investigative procedure. The trials used different time periods to report the long-term occurrence of major stroke: 5 years in the NASCET and a mean of 6 years in the ECST. Therefore, the rates of major stroke and death were adjusted downwards for the ECST data, assuming an equal risk of 2% in the sixth year between treatment groups. These combined estimated rates for people with 70–99% stenosis were:

- major stroke within 30 days of endarterectomy (non-disabling stroke 2.6%, disabling stroke 1.9%) and death (0.6%)
- major stroke within 32 days of initial medical management (non-disabling stroke 1.5%, disabling stroke 0.4%) and death (0.2%)
- major stroke within 5 years of endarterectomy (non-disabling stroke 25%, disabling stroke 5.4%) and death (7.9%)
- major stroke within 5 years of initial medical management (non-disabling stroke 29.7%, disabling stroke 13.8%) and death (6.8%).

These data were used to estimate the probability of events for patients with true-positive or false-negative test results for 70–99% stenosis. The data for false-positive and true-negative results were estimated from the reported rates of events in these two trials for patients with less than 70% stenosis or occlusion.

The derived probabilities estimated from these data are shown in *Table 26*. There were insufficient data to estimate separate probabilities of transient ischaemic attack or other adverse events not leading to death. The branches on the decision tree for these events were assigned probabilities of zero. This may underestimate the risks of events with cost and/or outcome implications. However, it is not clear whether it will bias the results against one diagnostic method or another. It is also in line with the approach taken by economic evaluations of endarterectomy.[289]

Utility of outcomes

The utilities associated with no stroke, non-disabling stroke and disabling stroke were obtained from one article.[290] This study used the Euroqol to measure the health status for 867 UK patients enrolled in the International Stroke Trial.[291] The authors used the population–time trade-off values to estimate the utility of the health states reported by patients. The utility values for International Stroke Trial patients were 0.31 (95% CI, 0.29 to 0.34) for dependent health states, 0.71 (95% CI, 0.68 to 0.74) for independent health states and 0.88 (95% CI, 0. 84 to 0.92) for recovered health states. The values for recovered and independent health states were averaged to give a value for

TABLE 26 *Derived probabilities of events for diagnosis of carotid stenosis*

Event	Derived probability of event		
	DSA	MRA	Ultrasound + MRA
Diagnosis-related stroke:	0.02	0.00	0.00
non-disabling	0.46	–	–
disabling	0.34	–	–
dead	0.20	–	–
No diagnosis-related stroke	0.98	1.00	1.00
Endarterectomy	0.21	0.25	0.37
Endarterectomy, true positive	1.00	0.92	0.97
Endarterectomy, false positive	0.00	0.08	0.03
Endarterectomy, true positive, die, 5 years	0.08	0.08	0.08
Endarterectomy, false positive, die, 5 years	0.06	0.06	0.06
Endarterectomy, true positive, disabling stroke, 5 years	0.05	0.05	0.05
Endarterectomy, false positive, disabling stroke, 5 years	0.06	0.06	0.06
Endarterectomy, true positive, non-disabling stroke, 5 years	0.25	0.25	0.25
Endarterectomy, false positive, non-disabling stroke, 5 years	0.21	0.21	0.21
Endarterectomy, true positive, no events, 5 years	0.62	0.62	0.62
Endarterectomy, false positive, no events, 5 years	0.67	0.67	0.67
No endarterectomy	0.79	0.76	0.63
No endarterectomy true negative	1.00	0.94	0.92
No endarterectomy false negative	0.00	0.06	0.08
No endarterectomy, true negative, die, 5 years	0.07	0.07	0.07
No endarterectomy, false negative, die, 5 years	0.11	0.11	0.11
No endarterectomy, true negative, disabling stroke, 5 years	0.06	0.06	0.06
No endarterectomy, false negative, disabling stroke, 5 years	0.13	0.13	0.13
No endarterectomy, true negative, non-disabling stroke, 5 years	0.21	0.21	0.21
No endarterectomy, false negative, non-disabling stroke, 5 years	0.23	0.23	0.23
No endarterectomy, true negative, no events, 5 years	0.66	0.66	0.66
No endarterectomy, false negative, no events, 5 years	0.53	0.53	0.53

the health state of non-disabling stroke used in the model. The values for the dependent health state were used for the health state of disabling stroke used in the model.

The mean utility values reported by Dorman and co-workers[290] were similar to those reported by the authors of smaller studies (fewer than 100 respondents).[292–295]

Resource use and costs

The estimates of resource use and cost, and the relevant sources of data are shown in *Table 27*. The data were estimated from:

- national statistics derived from UK hospital activity and costs data (costs of hospital admission for stroke, endarterectomy)
- one published study[296] that used an Office of Population Censuses and Surveys database of 5822 people to estimate the costs of cognitive and non-cognitive disability (long-term costs of stroke)
- local activity and accounts data (costs of DSA, MRA and ultrasound).

The costs of the diagnostic evaluations are summarised in *Table 28*. The initial purchase costs of capital equipment were estimated from list prices as £1.28 million for MRA (scanner, software and injector) and £602,500 for DSA (equipment and injector). Annual maintenance costs for the equipment were estimated as £72,600 for MRA and £31,636 for DSA. The average cost per minute for the equipment was estimated on the basis of 15 sessions per week of 4 hours per session and 50 weeks per year. The average cost per minute was £1.39 for MRA and £0.62 for DSA (local accounts estimate, see *Tables 27* and *28*). The capital cost per procedure was estimated

TABLE 27 *Resource use and costs of events associated with carotid stenosis*

Event	Unit costs, 2000 (£)			Average resource use	Average cost/event (£)
	Average	SD	Range		
DSA including capital equipment*	204	39	99*–986†	1.00	204
DSA excluding capital equipment*	186	28	98–221	1.00	186
MRA including capital equipment*	110	28	60–161	1.00	110
MRA excluding capital equipment*	54	20	22–102	1.00	54
MRA + ultrasound*	310	NA	259–361	1.00	310
Stroke:					
predischarge, inpatient stay†	1,619	NA	0–15,935	1.00	1,619
postdischarge, inpatient stay†	2,099	NA	45–16,415	1.00	2,099
Endarterectomy, inpatient day‡#	407	NA	169–690	6.00	2,442
Stroke disabled, per year§	10,525	NA	6,188–15,288	1.00	10,525

NA, not applicable

* *Leeds Teaching Hospitals NHS Trust*

† *Health Resource Groups 1998–1999, Department of Health 2001*

‡ *Personal Social Services Research Unit unit costs of care*[324]

§ *Costs of non-cognitive disability*[296]

\# *Hospital episode statistics (L29), 1998–1999*[325]

TABLE 28 *Detailed local costs of DSA and MRA for carotid artery stenosis*

	DSA			MRA		
	Mean	SD	Range	Mean	SD	Range
Staff time	36	28	13–136	40	16	10–78
Consumables	5	NA	NA	14	9	0–25
Equipment	18	10.83	6–56	56	10	38–76
Inpatient stay	144	NA	NA	0	0	0
Total	204	39	99–277	110	28	60–161

TABLE 29 *Expected long-term costs and QALYs of DSA and MRA for the diagnosis of carotid artery stenosis*

	DSA			MRA		
	Expected cost (£)	**Expected QALYs**	***p***	**Expected cost (£)**	**Expected QALYs**	***p***
Survive diagnosis, well, endarterectomy, true positive						
Alive well	338.43	0.97	0.13	354.40	1.06	0.14
Stroke, alive well	233.70	0.38	0.05	248.55	0.41	0.06
Stroke, alive disabled	832.78	0.04	0.01	903.66	0.05	0.01
Dead	76.13	0.03	0.02	80.96	0.04	0.02
Survive diagnosis, well, endarterectomy, false positive						
Alive well	0.00	0.00	0.00	33.70	0.10	0.01
Stroke, alive well	0.00	0.00	0.00	18.48	0.03	0.00
Stroke, alive disabled	0.00	0.00	0.00	90.79	0.00	0.00
Dead	0.00	0.00	0.00	5.39	0.00	0.00
Survive diagnosis, well, no endarterectomy, true negative						
Alive well	103.50	3.87	0.51	50.00	3.53	0.46
Stroke, alive well	346.15	1.21	0.17	301.23	1.11	0.15
Stroke, alive disabled	3311.76	0.18	0.05	3016.46	0.16	0.04
Dead	116.64	0.11	0.06	101.51	0.10	0.05
Survive diagnosis, well, no endarterectomy, false negative						
Alive well	0.00	0.00	0.00	2.76	0.20	0.03
Stroke, alive well	0.00	0.00	0.00	22.29	0.08	0.01
Stroke, alive disabled	0.00	0.00	0.00	438.45	0.02	0.01
Dead	0.00	0.00	0.00	10.49	0.01	0.01
Survive diagnosis, non-disabling stroke, endarterectomy, true positive						
Alive well	5.02	0.02	0.00	0.00	0.00	0.00
Stroke, alive well	2.83	0.00	0.00	0.00	0.00	0.00
Stroke, alive disabled	7.08	0.00	0.00	0.00	0.00	0.00
Dead	0.92	0.00	0.00	0.00	0.00	0.00
Survive diagnosis, non-disabling stroke, endarterectomy, false positive						
Alive well	0.00	0.00	0.00	0.00	0.00	0.00
Stroke, alive well	0.00	0.00	0.00	0.00	0.00	0.00
Stroke, alive disabled	0.00	0.00	0.00	0.00	0.00	0.00
Dead	0.00	0.00	0.00	0.00	0.00	0.00
Survive diagnosis, non-disabling stroke, no endarterectomy, true negative						
Alive well	9.68	0.06	0.00	0.00	0.00	0.00
Stroke, alive well	28.19	0.01	0.00	0.00	0.00	0.00
Stroke, alive disabled	1.93	0.00	0.00	0.00	0.00	0.00
Dead	0.00	0.00	0.00	0.00	0.00	0.00
Survive diagnosis, non-disabling stroke, no endarterectomy, false negative						
Alive well	0.00	0.00	0.00	0.00	0.00	0.00
Stroke, alive well	0.00	0.00	0.00	0.00	0.00	0.00
Stroke, alive disabled	0.00	0.00	0.00	0.00	0.00	0.00
Dead	28.19	0.00	0.00	0.00	0.00	0.00

continued

TABLE 29 contd *Expected long-term costs and QALYs of DSA and MRA for the diagnosis of carotid artery stenosis*

	DSA			MRA		
	Expected cost (£)	**Expected QALYs**	***p***	**Expected cost (£)**	**Expected QALYs**	***p***
Survive diagnosis, disabling stroke, no endarterectomy, true negative						
Alive disabled	421.81	0.01	0.01	0.00	0.00	0.00
Stroke, alive disabled	29.31	0.00	0.00	0.00	0.00	0.00
Dead	1.00	0.00	0.00	0.00	0.00	0.00
Survive diagnosis, disabling stroke, no endarterectomy, false negative						
Alive disabled	0.00	0.00	0.00	0.00	0.00	0.00
Stroke, alive disabled	0.00	0.00	0.00	0.00	0.00	0.00
Dead	0.00	0.00	0.00	0.00	0.00	0.00
Die diagnosis	0.72	0.00	0.00	0.00	0.00	0.00
Total	5873.33	6.90	1.00	5679.14	6.89	1.00
Difference (DSA – MRA)	194.19	0.01				

as the product of the cost per minute and the average length of the investigation (local activity data, see *Tables 27* and *28*). The estimate of 15 sessions per week may be regarded as the maximum for any piece of equipment, and is more likely to be achieved for MRA equipment than for DSA equipment. This means that the analysis gives the minimum capital cost per evaluation. If the number of sessions is lower, as they may be for DSA, then the costs per evaluation are correspondingly higher. The analysis is thus a conservative one, which may be biased against MRA. The costs of capital expenditure were included in the equipment costs for the primary analysis and the sensitivity analyses. The ECST and NASCET trials indicated that medical management of patients was similar in the surgery and control groups, and management costs were excluded from this analysis.

Expected costs and outcomes

The detailed probabilities, long-term expected costs and QALYs for DSA and MRA are given in *Table 29*. Over the 10 years from diagnosis, DSA is expected to cost £194 more than MRA, with no difference in expected QALYs.

The results of the simulation and sensitivity analyses are summarised in *Table 30*. These results show a similar picture to those given in *Table 29,* with a higher cost associated with DSA than with MRA. The 95% CIs on the expected cost differences are positive, suggesting that this higher cost is statistically significant.

The exception is for MRA combined with ultrasound, which is more expensive than DSA used alone, and has a slightly lower expected QALY outcome. The 95% CIs on the differences in expected costs and QALYs suggest a statistically significant difference. This is mainly due to the additional 16–18% of cases where the tests disagree and DSA is used to confirm the diagnosis. Furthermore, the sensitivity and specificity for this combined option are less robust than those for MRA alone.

We also compared MRA alone with MRA plus ultrasound, to give a preliminary indication of the expected costs and benefits for those people not suitable for DSA. The expected costs of the combined option are higher than those for MRA alone, with no difference in expected QALYs.

What is the cost-effectiveness if MRA were purchased solely for the diagnosis and management of carotid artery disease?

Purchasers of MRA equipment need to decide in which diagnostic technique to invest capital funds. The capital costs of MRA and DSA were included in the primary analysis and sensitivity analyses reported above. These were based on local activity data (see *Tables 27* and *28*). Local data and expert opinion indicated that it was unlikely that the number and length of evaluations would provide sufficient throughput to justify the purchase of MRA equipment for the diagnosis and management of carotid artery disease alone. It was assumed that MRA equipment would also be

TABLE 30 *Summary of long-term expected costs and QALYs of DSA and MRA for diagnosis of carotid artery stenosis*

Analysis	DSA		MRA		Difference	
	Expected cost (£)	Expected QALYs	Expected cost (£)	Expected QALYs	Expected cost (£)	Expected QALYs
Base case						
Mean	5875.85	6.92	5686.14	6.91	189.71	0.01
5% CI	5858.88	6.89	5670.06	6.88	181.70	0.01
95% CI	5892.81	6.94	5702.21	6.93	197.72	0.01
Studies meeting inclusion criteria A–D						
Mean	5872.78	6.90	5561.25	6.90	311.53	0.00
5% CI	5855.97	6.88	5545.71	6.88	303.81	0.00
95% CI	5889.59	6.93	5576.79	6.93	319.25	0.00
6% discount rate, QALYs						
Mean	5881.82	5.54	5679.14	5.53	202.67	0.01
5% CI	5864.79	5.52	5663.05	5.51	194.80	0.00
95% CI	5898.84	5.56	5695.23	5.55	210.55	0.01
SROC analysis, $Q^* = 0.98$ (0.93 – 1)						
Mean	5872.53	6.90	5509.30	6.91	363.23	0.00
5% CI	5855.61	6.88	5493.89	6.88	355.51	–0.01
95% CI	5889.44	6.93	5524.71	6.93	370.94	0.00
SROC analysis, $Q^* = 0.99$ (0.97 – 1)						
Mean	5857.94	6.89	5471.03	6.90	386.91	–0.01
5% CI	5841.15	6.87	5455.66	6.88	379.29	–0.01
95% CI	5874.72	6.92	5486.40	6.93	394.53	–0.01
MRA plus ultrasound						
Mean	5879.39	6.90	6169.21	6.89	–289.82	0.02
5% CI	5862.19	6.88	6153.13	6.86	–296.22	0.01
95% CI	5896.59	6.93	6185.30	6.91	–283.42	0.02
Equal 5-year probability of disabling stroke/death endarterectomy and medical management						
Mean	7002.51	6.86	6851.72	6.85	150.79	0.01
5% CI	6981.51	6.84	6831.67	6.82	141.04	0.01
95% CI	7023.51	6.88	6871.77	6.87	160.55	0.02
	MRA		**MRA + ultrasound**		**Difference**	
	Expected cost (£)	Expected QALYs	Expected cost (£)	Expected QALYs	Expected cost (£)	Expected QALYs
MRA versus MRA + ultrasound						
Mean	5677.19	6.89	6165.46	6.89	–492.03	0.01
5% CI	5661.16	6.87	6149.30	6.86	–498.17	0.00
95% CI	5693.21	6.92	6181.62	6.91	–485.88	0.01

used for evaluation of patients without carotid artery disease and so be fully utilised. If the use of the equipment varies substantially between locations, then the expected costs will also vary. The expected costs and outcomes of MRA and DSA for different levels of activity associated with the equipment are given in *Table 31*.

These data indicate that if the relevant equipment is used (for patients with and without carotid artery disease) at 10% of full capacity or less then the full expected costs of DSA are lower than those of MRA. If the utilisation rate is greater than 10% (for patients with and without carotid artery disease) then, as in the other

TABLE 31 *Impact of capital costs and throughput: DSA versus MRA for carotid artery stenosis*

Utilisation rate (%)	DSA (£)		MRA (£)		Expected difference in cost (DSA – MRA) (£)
	Cost	Expected cost	Cost	Expected cost	
10	368	6037	613	6184	–147
20	277	5947	333	5904	42
30	246	5916	240	5811	104
40	231	5901	194	5765	135
50	222	5892	166	5737	154
60	216	5886	147	5718	167
70	212	5882	134	5705	176
80	208	5878	125	5696	181
90	206	5876	116	5687	188
100 (base case)	204	5873	110	5679	194

analyses, MRA is associated with a lower expected cost than DSA.

What is the optimal assessment strategy for a patient presenting with carotid artery disease?
If the clinician wishes to maximise the long-term expected outcomes of treatment, the analyses indicate that there is no statistically significant difference between MRA alone or DSA. MRA is the lower cost option. This also holds true when capital costs are excluded from the costs of the procedure (–£230). The choice would then need to be made on the preferences of the clinician (and if applicable the patient) for the process of an uncomfortable invasive test with a risk of stoke (DSA) or a non-invasive test (MRA). If the clinician and patient are prepared to incur the additional costs and procedure, MRA plus ultrasound would give additional health gains of around 1 QALY at an expected cost of £1281. However, this would also carry the chance of an additional invasive investigation (DSA) for around 16–18% of patients.

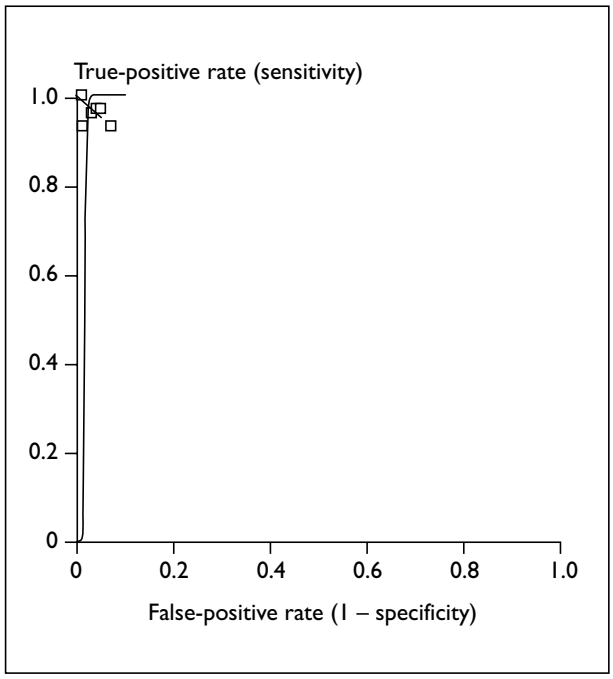

FIGURE 14 *Peripheral vascular disease: SROC curve for contrast-enhanced MRA, 0–49% versus 50–100% (number of studies included = 6). The straight line shows the 95% CI for Q^*; there are no overlapping points*

Peripheral vascular disease

Compared with the gold standard of X-ray angiography, what is the diagnostic accuracy of contrast-enhanced MRA techniques for identifying the severity of peripheral vascular disease?

0–49% versus 50–100%

Results from six studies[95,133,135,136,139,140] were included in the meta-analysis. The SROC curve (*Figure 14*) has Q^* = 0.98 (95% CI, 0.95 to 1.00).

0–49% or 100% versus 50–99%

Only four articles[95,135,139,140] used the 0–49% or 100% versus 50–99% dichotomy. These results are presented in *Table 18*. The sensitivity was slightly lower here than for the 0–49% versus 50–100% dichotomy.

0–99% versus 100%

Results from five articles[37,95,135,139,140] were included in the meta-analysis. A SROC curve could not be fitted to the data because the slope

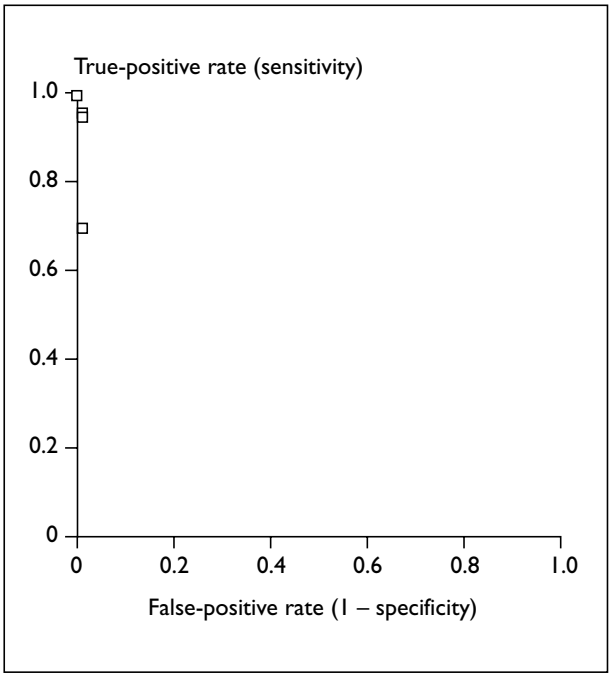

FIGURE 15 *Peripheral vascular disease: results for contrast enhanced MRA, 0–99% versus 100% (number of studies included = 5). A SROC could not be fitted to these data; two points coincide at (0, 1)*

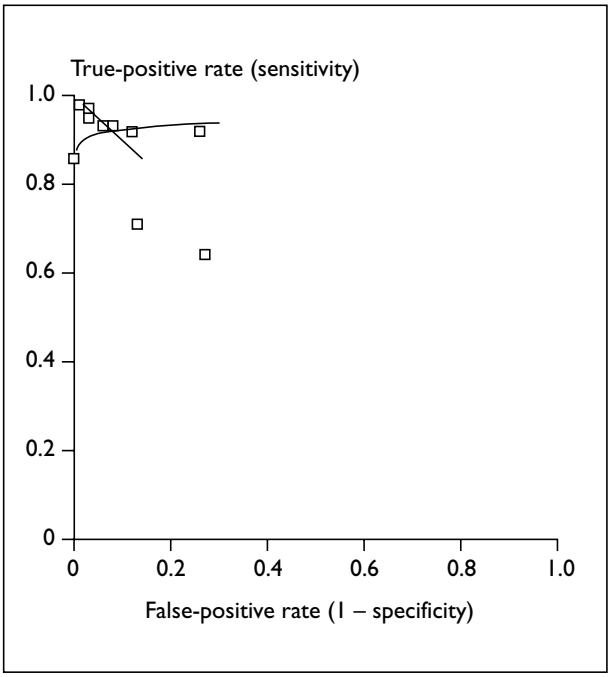

FIGURE 16 *Peripheral vascular disease: SROC curve for 2D TOF MRA, 0–49% versus 50–100% (number of studies included = 10). The straight line shows the 95% CI for Q^*; there are no overlapping points*

of the fitted line was outside the allowable range. The individual results are plotted without a fitted curve in *Figure 15*.

Compared with the gold standard of X-ray angiography, what is the diagnostic accuracy of 3D TOF MRA techniques for identifying the severity of peripheral vascular disease?

Only one[128] of the studies included in the review used 3D TOF techniques without contrast enhancement. This assessed vessels below the knee. The results were not considered separately from the contrast-enhanced MRA results.

Compared with the gold standard of X-ray angiography, what is the diagnostic accuracy of 2D TOF MRA techniques for identifying the severity of peripheral vascular disease?

0–49% versus 50–100%

Results from ten articles[82,93,127,129,131,132,134,135,137,141] were included in the meta-analysis. The SROC curve (*Figure 16*) has Q^* = 0.92 (95% CI, 0.86 to 0.98).

0–49% or 100% versus 50–99%

Results from nine articles[82,93,127,129,131,134,135,141] were included in the meta-analysis. The SROC curve (*Figure 17*) has Q^* = 0.80 (95% CI, 0.55 to 1.00).

0–99% versus 100%

Results from ten articles[82,92,93,127,129–131,134,135,141] were included in the meta-analysis. The SROC curve (*Figure 18*) has Q^* = 0.98 (95% CI, 0.95 to 1.00).

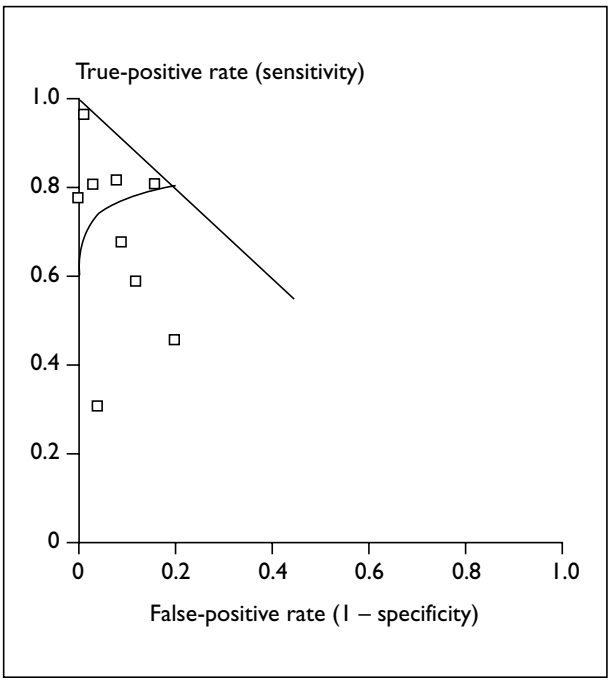

FIGURE 17 *Peripheral vascular disease: SROC curve for 2D TOF MRA, 0–49% or 100% versus 50–99% (number of studies included = 9). The straight line shows the 95% CI for Q^*; there are no overlapping points*

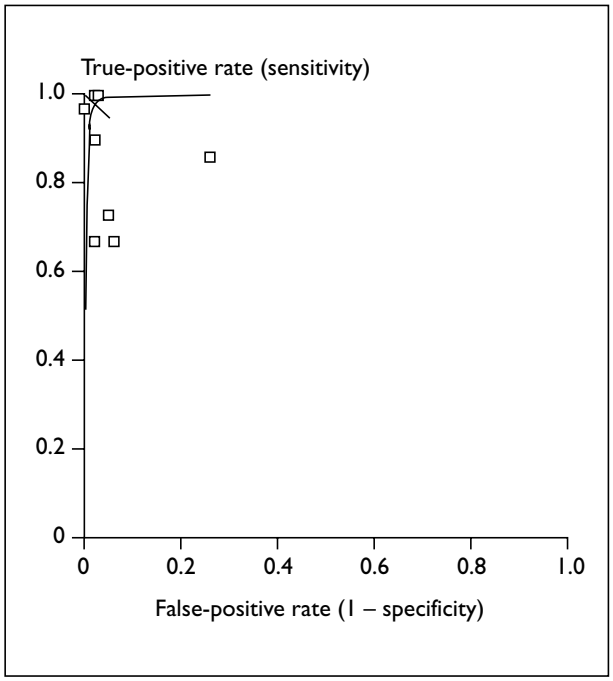

FIGURE 18 *Peripheral vascular disease: SROC curve for 2D TOF MRA, 0–99% versus 100% (number of studies included = 10). The straight line shows the 95% CI for Q*; there are two overlapping points at (0.02, 1) and at (0, 0.97)*

Results for arteries above and below the knee are compared as part of the sensitivity analysis in chapter 7.

Compared with the gold standard of X-ray angiography, what is the diagnostic accuracy of phase-contrast MRA techniques for identifying the severity of peripheral vascular disease?

Only one[138] article using phase-contrast MRA was included in the review. Steffens and co-workers[138] used 2D phase-contrast MRA. They reported a sensitivity of 98% and a specificity of 83% for diagnosing 0–49% versus 50–100%. They did not compare phase-contrast MRA with other MRA techniques, but this result has a lower specificity than the results using 2D TOF that had a comparable sensitivity (see *Figure 16*).

What are the long-term costs and outcomes of MRA and conventional angiography in the diagnosis and management of patients presenting with peripheral vascular disease?

Probability of events

The data on the sensitivity and specificity of MRA were derived from the 15 articles included in the systematic review for stenoses of 0–49% versus 50–100%.[82,93,95,127,129,131–137,139–141] The data for 2D TOF and contrast-enhanced MRA were combined. This approach was taken to increase the generalisability of the analysis to different settings, as the results of the survey indicated that a range of MRA techniques is available and used in the UK. The results for MRA show a high level of sensitivity (94%) and specificity (overall 93%). The probabilities of positive or negative MRA tests were also estimated from these articles. The sensitivity analysis used the high and low estimates of sensitivity (93% to 100%, contrast-enhanced MRA; 64–100%, 2D TOF MRA) and specificity (93% to 100%, contrast-enhanced MRA; 73–100%, 2D TOF MRA) derived from the systematic review. For the sensitivity analysis, the probability of surgery following DSA was estimated as the prevalence of 50–100% stenosis in the trial population (25%). The probability of surgery following MRA was estimated as the proportion of patients diagnosed with this degree of stenosis by MRA (28%).

In the model, comparison was made between DSA and MRA, where each study is followed by intraoperative arteriography. This is not normal clinical practice, but data were available in the literature to populate the tree. The probability that preoperative evaluation is concordant with intraoperative arteriography (94% ± 10% for DSA, 92% ± 10% MRA for bypass and amputation; 98% ± 10% for percutaneous transluminal angioplasty, MRA and DSA equal) was estimated from one study[83] not included in the systematic review, which compared detailed treatment plans with actual procedures. This study was also used to estimate the probability of type of procedure following inaccurate surgical planning. The derived probability of these events is shown in *Table 32*.

Five papers were used to estimate the probability of patency following bypass (best estimate 77%, range 36–87%) and percutaneous transluminal angioplasty (best estimate 67%, range 46–97%), the probability that a patient was ambulant following amputation (best estimate 56%, range 30–100%) and death.[79–81,297,298] These figures represent pooled results for all sites and types of procedure. A lack of evidence on mobility outcomes led to an approximation for the probability that a patient was ambulant following bypass surgery or percutaneous transluminal angioplasty. This probability was set to equal the patency rate of the procedure. The probability for each health state, given whether or not the patient was alive and ambulant, or alive and not ambulant, were estimated from one study.[298]

TABLE 32 *Derived probabilities of events for assessment of peripheral vascular disease*

Event	Derived probability of event	
	DSA	**MRA**
Patient has < 50% stenosis	0.75	0.75
Patient has 50–100% stenosis	0.25	0.25
Plan surgery or PTA:	0.25	0.28
accurate, stenosis 50–100%	1.00	0.94
inaccurate, stenosis < 50%	0.00	0.06
Plan bypass:	0.69	0.69
accurate plan	0.94	0.92
inaccurate, no IOA, continue bypass	0.00	0.00
inaccurate, change type of bypass	0.06	0.02
inaccurate, change to amputation	0.01	0.01
inaccurate, change to PTA	0.00	0.06
inaccurate, < 50% stenosis, continue	0.00	0.00
inaccurate, < 50% stenosis, medical management	0.00	1.00
Plan PTA:	0.23	0.23
accurate plan	0.98	0.98
inaccurate, no IOA, continue PTA	0.00	0.00
inaccurate, change to amputation	0.02	0.00
inaccurate, change to bypass	0.00	0.02
inaccurate, < 50% stenosis, continue	0.00	0.00
inaccurate, < 50% stenosis, medical management	0.00	1.00
Plan amputation:	0.08	0.08
accurate plan	0.94	0.92
inaccurate, no IOA, continue amputation	0.00	0.00
inaccurate, change to bypass	0.06	0.06
inaccurate, change to PTA	0.01	0.02
inaccurate, < 50% stenosis, continue	0.00	0.00
inaccurate, < 50% stenosis, medical management	0.00	1.00
Plan medical management:	0.75	0.72
accurate plan, stenosis < 50%	1.00	0.93
inaccurate plan, stenosis 50–100%	0.00	0.07
Stenosis 50–100%, amputation		
Full mobility	0.03	0.03
Limited mobility, independent	0.18	0.18
Limited mobility, dependent	0.20	0.20
Wheelchair	0.32	0.32
Bedridden	0.01	0.01
Dead	0.25	0.25
Stenosis 50–100%, bypass		
Full mobility	0.05	0.05
Limited mobility, independent	0.29	0.29
Limited mobility, dependent	0.32	0.32
Wheelchair	0.19	0.19
Bedridden	0.01	0.01
Dead	0.14	0.14

continued

TABLE 32 contd *Derived probabilities of events for assessment of peripheral vascular disease*

Event	Derived probability of event	
	DSA	**MRA**
Stenosis 50–100%, PTA		
Full mobility	0.05	0.05
Limited mobility, independent	0.26	0.26
Limited mobility, dependent	0.29	0.29
Wheelchair	0.28	0.28
Bedridden	0.01	0.01
Dead	0.11	0.11
Stenosis 50–100%, medical management		
Full mobility	0.03	0.03
Limited mobility, independent	0.18	0.18
Limited mobility, dependent	0.20	0.20
Wheelchair	0.32	0.32
Bedridden	0.01	0.01
Dead	0.25	0.25
Stenosis < 50%, amputation		
Full mobility	0.03	0.03
Limited mobility, independent	0.18	0.18
Limited mobility, dependent	0.20	0.20
Wheelchair	0.32	0.32
Bedridden	0.01	0.01
Dead	0.25	0.25
Stenosis < 50%, bypass		
Full mobility	0.06	0.06
Limited mobility, independent	0.33	0.33
Limited mobility, dependent	0.36	0.36
Wheelchair	0.14	0.14
Bedridden	0.00	0.00
Dead	0.11	0.11
Stenosis < 50%, PTA		
Full mobility	0.07	0.07
Limited mobility, independent	0.37	0.37
Limited mobility, dependent	0.40	0.40
Wheelchair	0.15	0.15
Bedridden	0.00	0.00
Dead	0.00	0.00
Stenosis < 50%, medical management		
Full mobility	0.07	0.07
Limited mobility, independent	0.37	0.37
Limited mobility, dependent	0.40	0.40
Wheelchair	0.16	0.16
Bedridden	0.00	0.00
Dead	0.00	0.00

IOA, intraoperative arteriography

Overall, this review of costs and outcomes of treatment for peripheral vascular disease, in common with others (two of which were undertaken at the same time as this work), found that the evidence to estimate the probabilities of long-term outcomes was limited and highly uncertain.[79–81] The derived probability of these events is shown in *Table 32*.

Utility of outcomes

The utilities associated with different levels of mobility were adapted from those reported in one study.[79] This study used the standard gamble to measure the health status for a sample (110 completed interviews of the general public in the UK). The utility values were 0.32 (95% CI, 0.26 to 0.39) for confined to bed, 0.45 (95% CI, 0.41 to 0.5) for wheelchair use, 0.7–0.79 for the health state limited ambulant and independent, and 0.56–0.7 for the health state limited ambulant and dependent. In the absence of any data, the health state fully ambulant was estimated from the overall population level (mean 0.86, standard deviation = 0.23) reported by Kind and co-workers.[299] The derived utility and QALY values used in the analysis are shown in *Table 33*.

Resource use and costs

The estimates (average and range) of resource use and cost and sources of data are given in *Tables 34* and *35*. The costs of the diagnostic evaluations, estimated as the cost per minute of the equipment and the cost of consumables, are reported above for carotid artery disease (see *Table 28*). The cost per evaluation was estimated as the cost per minute multiplied by the average time per evaluation. The costs of consumables and equipment were added to the examination time-dependent staff costs (£119 for DSA, £108 for MRA) for the evaluation of peripheral vascular disease.

TABLE 33 *Utility values of health states following treatment of peripheral vascular disease*

Health state	Utility values
Full mobility:	0.83
amputation	NA
critical limb ischaemia	0.83
claudication	0.83
Limited mobility, independent:	
amputation	0.56
critical limb ischaemia	0.73
claudication	0.78
Limited mobility, dependent:	
amputation	0.56
critical limb ischaemia	0.69
claudication	0.69
Wheelchair, dependent	0.46
Bedridden	0.33
Dead	0.00

TABLE 34 *Unit costs of events associated with peripheral vascular disease*

Unit costs	Average (£)	Range (£)
DSA, including capital equipment*	455	400–651
DSA, excluding capital equipment*	418	334–502
MRA, including capital equipment*	247	416–464
MRA, excluding capital equipment*	122	98–146
Inpatient care costs†		
Theatre time, per minute	8	7–8
Intensive care unit per hour	1,155	1,047–1,262
High dependency unit per hour	449	447–451
Other inpatient ward per day	195	183–207
Long-term costs‡		
Full mobility	0	0
Limited mobility, independent	713	0–1,425
Limited mobility, dependent	6,738	1,425–12,051
Wheelchair‡§	12,172	10,525–13,818
Bedridden§	20,472	13,818–27,125

* *Estimated from Leeds Teaching Hospitals NHS Trust activity data*
† *Michaels and co-workers*[79]
‡ *Netten and Curtis*[324]
§ *Kavanagh and Knapp*[296]

All the resource use and costs for the hospital admission for surgery and percutaneous transluminal angioplasty were estimated from those reported by Michaels and co-workers[79] for hospitals in the Trent region (*Table 36*). This is the only UK published paper to report detailed and up to date information based on actual activity data. The main alternative source of information to this study was from the National Hospital Episode Statistics and Health Resource Groups.[300,301] Unlike carotid artery disease, where there is a specific code for carotid endarterectomy, the classifications for peripheral vascular interventions in the national data include a large number of codes, which incorporate conditions and procedures not included in our peripheral vascular disease model.

TABLE 35 *Resource use associated with peripheral vascular disease*

Resource use	Average	Range
DSA, including capital equipment*	1	No range
MRA, including capital equipment*	1	No range
Amputation†		
Above knee, primary:		
theatre time (minutes)	125	100–150
intensive care unit (hours)	6	5–7
high dependency unit (hours)	4	3–5
other inpatient ward (days)	23	21–25 (95% CI)
Above knee plan changed to bypass:		
theatre time (minutes)	312	No range
intensive care unit (hours)	4	4–5
high dependency unit (hours)	4	3–4
other inpatient ward (days)	14	14–25
Above knee revision, readmission:		
theatre time (minutes)	114	83–144
intensive care unit (hours)	6	5–7
high dependency unit (hours)	4	3–5
other inpatient ward (days)	23	21–25 (95% CI)
Below knee primary:		
theatre time (minutes)	156	125–187
intensive care unit (hours)	6	5–7
high dependency unit (hours)	4	3–5
other inpatient ward (days)	23	21–25 (95% CI)
Below knee plan changed to bypass:		
theatre time (minutes)	312	No range
intensive care unit (hours)	4	4–5
high dependency unit (hours)	4	3–4
other inpatient ward (days)	14	14–25
Below knee revision, readmission:		
theatre time (minutes)	114	83–144
intensive care unit (hours)	6	5–7
high dependency unit (hours)	4	3–5
other inpatient ward (days)	23	21–25 (95% CI)
Bypass†		
Bypass primary:		
theatre time (minutes)	199	190–318
intensive care unit (hours)	4	4–5
high dependency unit (hours)	4	3–4
other inpatient ward (days)	14	14–25
Bypass plan changed to amputation:		
theatre time (minutes)	199	190–318
intensive care unit (hours)	4	4–5
high dependency unit (hours)	4	3–4
other inpatient ward (days)	14	14–25
Bypass plan changed to PTA:		
theatre time (minutes)	199	190–318
intensive care unit (hours)	0	No range
high dependency unit (hours)	0	No range
other inpatient ward (days)	3	2–3 (95% CI)
Bypass revision, readmission:		
theatre time (minutes)	199	190–318
intensive care unit (hours)	4	4–5
high dependency unit (hours)	4	3–4
other inpatient ward (days)	14	14–25
Percutaneous transluminal angioplasty†		
PTA primary:		
theatre time (minutes)‡	63	50–75
intensive care unit (hours)	0	No range
high dependency unit (hours)	0	No range
other inpatient ward (days)	3	2–3 (95% CI)
PTA plan changed to bypass:		
theatre time (minutes)‡	261	No range
intensive care unit (hours)	4	4–5
high dependency unit (hours)	4	3–4
other inpatient ward (days)	14	14–25
PTA plan changed to amputation:		
theatre time (minutes)‡	219	No range
intensive care unit (hours)	6	5–7
high dependency unit (hours)	4	3–5
other inpatient ward (days)	23	21–25 (95% CI)
PTA revision, readmission:		
theatre time (minutes)‡	63	50–75
intensive care unit (hours)	0	No range
high dependency unit (hours)	0	No range
other inpatient ward (days)	3	2–3 (95% CI)
Long-term costs		
Full mobility	1	No range
Limited mobility, independent	1	No range
Limited mobility, dependent	1	No range
Wheelchair	1	No range
Bedridden	1	No range

* *Estimated from Leeds Teaching Hospitals NHS Trust activity data*
† *Estimated from Michaels and co-workers*[79]
‡ *Estimated values*

TABLE 36 *Costs of events associated with peripheral vascular disease*

	Cost per event (£)
DSA, including capital equipment	455
MRA, including capital equipment	247
Amputation*	
Above knee primary	5,825
Above knee plan changed to bypass	5,370
Above knee revision, readmission	5,738
Below knee primary	6,059
Below knee plan changed to bypass	5,370
Below knee revision, readmission	5,738
Bypass*	
Bypass primary	4,514
Bypass plan changed to amputation	4,514
Bypass plan changed to PTA	2,032
Bypass revision, readmission	4,514
Percutaneous transluminal angioplasty*	
PTA, primary	1,003
PTA plan changed to bypass	4,985
PTA plan changed to amputation	6,530
PTA revision, readmission	1,003
Long-term costs	
Full mobility	0
Limited mobility, independent	713
Limited mobility, dependent	6,738
Wheelchair	12,172
Bedridden	20,472

* *Michaels and co-workers*[79]

Expected costs and outcomes

The detailed probabilities, 1-year expected costs and QALYs for DSA and MRA diagnostic evaluations to plan treatment for peripheral vascular disease are given in *Table 37*. There were no differences in the expected costs or QALYs between DSA and MRA.

Table 38 summarises the results of the simulation and sensitivity analyses. The sensitivity analyses indicate that DSA is associated with a higher expected cost than MRA in most cases, with similar expected QALYs. The exceptions to this are as follows:

- If DSA is compared to 2D TOF MRA, the expected cost of DSA is lower.
- If the sensitivity and specificity data for contrast-enhanced MRA only are used, then DSA and MRA are of similar expected outcome, but the expected cost of MRA is between £6 (mean sensitivity and specificity of MRA) and £55 (SROC analysis, $Q^* = 0.98$) lower.

What is the cost-effectiveness if MRA were purchased solely for the diagnosis and management of peripheral vascular disease?
Purchasers of MRA equipment need to decide in which diagnostic technique to invest capital funds. The capital costs of MRA and DSA were included in the primary analysis and sensitivity analyses reported above. These were based on local activity data (see *Tables 27* and *28*) and assumed that the equipment would be fully utilised. If the use of the equipment varies substantially between locations, then the expected costs will also vary. The expected costs and outcomes of MRA and DSA for different levels of activity associated with the equipment are presented in *Table 39*.

These data indicate that, if the utilisation rate of the relevant equipment is less than 100%, DSA is associated with lower expected costs than MRA. The net expected savings associated with DSA range from £845 per person when the equipment is used at 10% of capacity, down to £9 per person when the equipment is used at 90% of capacity.

What is the optimal assessment strategy for a patient presenting with peripheral vascular disease?
If the clinician wishes to maximise the 1-year expected outcomes of treatment, the analyses indicate that there is no statistically significant difference between MRA and DSA. According to this analysis, DSA is the lower cost option if 2D TOF is used, but MRA is the lower cost option if contrast-enhanced MRA is available. However, if both DSA and MRA are available in the local setting, the capital costs of investment in the equipment are effectively zero in the short term. In this case, where capital costs are excluded from the costs of the evaluation then MRA is associated with a lower expected cost than DSA (–£136).

The apparent lack of differences in outcome between DSA and MRA suggests that the choice between them will depend on the equipment available locally and the preferences of the clinician (and, if appropriate, the patient). The choice is between the process and small potential additional risk of an invasive test (DSA), or the process of a less sensitive and less accurate but non-invasive test (MRA).

TABLE 37 *Expected long-term costs and QALYs of DSA and MRA for the assessment of peripheral vascular disease*

	DSA			MRA		
	Expected costs (£)	**Expected QALYs**	***p***	**Expected costs (£)**	**Expected QALYs**	***p***
Plan bypass, stenosis 50–100%, accurate plan						
Full mobility	42	0.01	0.01	42	0.01	0.01
Limited mobility, independent	263	0.03	0.05	263	0.03	0.05
Limited mobility, dependent	592	0.03	0.05	603	0.03	0.05
Wheelchair	523	0.01	0.03	536	0.01	0.03
Bedridden	24	0.00	0.00	25	0.00	0.00
Dead	111	0.00	0.02	110	0.00	0.02
Plan bypass, stenosis 50–100%, inaccurate plan, no IOA, continue bypass						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	0	0.00	0.00
Wheelchair	0	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan bypass, stenosis 50–100%, inaccurate plan, change bypass						
Full mobility	3	0.00	0.00	1	0.00	0.00
Limited mobility, independent	17	0.00	0.00	5	0.00	0.00
Limited mobility, dependent	38	0.00	0.00	12	0.00	0.00
Wheelchair	34	0.00	0.00	11	0.00	0.00
Bedridden	2	0.00	0.00	1	0.00	0.00
Dead	7	0.00	0.00	2	0.00	0.00
Plan bypass, stenosis 50–100%, inaccurate plan, change to PTA						
Full mobility	0	0.00	0.00	1	0.00	0.00
Limited mobility, independent	0	0.00	0.00	8	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	26	0.00	0.00
Wheelchair	0	0.00	0.00	42	0.00	0.00
Bedridden	0	0.00	0.00	2	0.00	0.00
Dead	0	0.00	0.00	3	0.00	0.00
Plan bypass, stenosis 50–100%, inaccurate plan, amputation						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	1	0.00	0.00	1	0.00	0.00
Limited mobility, dependent	2	0.00	0.00	3	0.00	0.00
Wheelchair	5	0.00	0.00	6	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	1	0.00	0.00	1	0.00	0.00
Plan bypass, stenosis < 50%, inaccurate plan, continue bypass						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	0	0.00	0.00
Wheelchair	0	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00

continued

TABLE 37 contd *Expected long-term costs and QALYs of DSA and MRA for the assessment of peripheral vascular disease*

	DSA			MRA		
	Expected costs (£)	**Expected QALYs**	***p***	**Expected costs (£)**	**Expected QALYs**	***p***
Plan bypass, stenosis < 50%, inaccurate plan, medical management						
Full mobility	0	0.00	0.00	4	0.00	0.00
Limited mobility, independent	0	0.00	0.00	23	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	53	0.00	0.00
Wheelchair	0	0.00	0.00	30	0.00	0.00
Bedridden	0	0.00	0.00	1	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan PTA, stenosis 50–100%, accurate plan						
Full mobility	4	0.00	0.00	3	0.00	0.00
Limited mobility, independent	31	0.01	0.01	30	0.01	0.02
Limited mobility, dependent	127	0.01	0.02	131	0.01	0.02
Wheelchair	211	0.01	0.02	219	0.01	0.02
Bedridden	10	0.00	0.00	11	0.00	0.00
Dead	9	0.00	0.01	8	0.00	0.01
Plan PTA, stenosis 50–100%, inaccurate plan, no IOA, continue PTA						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	0	0.00	0.00
Wheelchair	0	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan PTA, stenosis 50–100%, inaccurate plan, bypass						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	2	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	4	0.00	0.00
Wheelchair	0	0.00	0.00	3	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	1	0.00	0.00
Plan PTA, stenosis 50–100%, inaccurate plan, amputation						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	1	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	3	0.00	0.00	0	0.00	0.00
Wheelchair	6	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	2	0.00	0.00	0	0.00	0.00
Plan PTA, stenosis < 50%, inaccurate plan, continue PTA						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	0	0.00	0.00
Wheelchair	0	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00

continued

TABLE 37 contd *Expected long-term costs and QALYs of DSA and MRA for the assessment of peripheral vascular disease*

	DSA			MRA		
	Expected costs (£)	**Expected QALYs**	***p***	**Expected costs (£)**	**Expected QALYs**	***p***
Plan PTA, stenosis < 50%, inaccurate plan, medical management						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	3	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	12	0.00	0.00
Wheelchair	0	0.00	0.00	8	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan amputation, stenosis 50–100%, accurate plan						
Full mobility	4	0.00	0.00	4	0.00	0.00
Limited mobility, independent	24	0.00	0.00	25	0.00	0.00
Limited mobility, dependent	49	0.00	0.00	50	0.00	0.00
Wheelchair	110	0.00	0.01	113	0.00	0.01
Bedridden	5	0.00	0.00	5	0.00	0.00
Dead	30	0.00	0.00	30	0.00	0.00
Plan amputation, stenosis 50–100%, inaccurate plan, no IOA, continue amputation						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	0	0.00	0.00
Wheelchair	0	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan amputation, stenosis 50–100%, inaccurate plan, bypass						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	2	0.00	0.00	2	0.00	0.00
Limited mobility, dependent	5	0.00	0.00	5	0.00	0.00
Wheelchair	4	0.00	0.00	4	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	1	0.00	0.00	1	0.00	0.00
Plan amputation, stenosis 50–100%, inaccurate plan, PTA						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	1	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	2	0.00	0.00
Wheelchair	1	0.00	0.00	2	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan amputation, stenosis < 50%, inaccurate plan, no IOA, continue amputation						
Full mobility	0	0.00	0.00	0	0.00	0.00
Limited mobility, independent	0	0.00	0.00	0	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	0	0.00	0.00
Wheelchair	0	0.00	0.00	0	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00

continued

TABLE 37 contd *Expected long-term costs and QALYs of DSA and MRA for the assessment of peripheral vascular disease*

	DSA			MRA		
	Expected costs (£)	**Expected QALYs**	***p***	**Expected costs (£)**	**Expected QALYs**	***p***
Plan amputation, stenosis < 50%, inaccurate plan, medical management						
Full mobility	0	0.00	0.00	1	0.00	0.00
Limited mobility, independent	0	0.00	0.00	3	0.00	0.00
Limited mobility, dependent	0	0.00	0.00	7	0.00	0.00
Wheelchair	0	0.00	0.00	4	0.00	0.00
Bedridden	0	0.00	0.00	0	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan medical management, stenosis < 50%, accurate plan						
Full mobility	23	0.04	0.05	11	0.04	0.05
Limited mobility, independent	326	0.19	0.28	240	0.17	0.25
Limited mobility, dependent	2190	0.20	0.30	1906	0.18	0.27
Wheelchair	1480	0.05	0.12	1304	0.05	0.11
Bedridden	76	0.00	0.00	67	0.00	0.00
Dead	0	0.00	0.00	0	0.00	0.00
Plan medical management, stenosis 50–100%, inaccurate plan						
Full mobility	0	0.00	0.00	7	0.00	0.00
Limited mobility, independent	0	0.00	0.00	11	0.01	0.01
Limited mobility, dependent	0	0.00	0.00	84	0.01	0.01
Wheelchair	0	0.00	0.00	198	0.01	0.02
Bedridden	0	0.00	0.00	10	0.00	0.00
Dead	0	0.00	0.00	46	0.00	0.01
Total	6396	0.61	1.00	6395	0.59	1.00
Difference (DSA – MRA)	1	0.01				

TABLE 38 *Summary of long-term expected costs and QALYs of DSA and MRA for the diagnosis of peripheral vascular disease*

	DSA		MRA		Difference, DSA – MRA	
	Expected costs (£)	**Expected QALYs**	**Expected costs (£)**	**Expected QALYs**	**Expected costs (£)**	**Expected QALYs**
Base case:						
mean	6,396.60	0.61	6,394.19	0.60	2.41	0.01
5% CI	6,371.61	0.61	6,369.84	0.59	–4.65	0.01
95% CI	6,421.59	0.61	6,418.54	0.60	9.47	0.01
Contrast-enhanced MRA only:						
mean	6,396.61	0.61	6,314.57	0.60	82.04	0.01
5% CI	6,371.68	0.61	6,290.11	0.60	75.15	0.01
95% CI	6,421.54	0.61	6,339.04	0.60	88.92	0.01
SROC, contrast-enhanced MRA, $Q^* = 0.98$:						
mean	6,395.22	0.61	6,243.15	0.60	152.06	0.00
5% CI	6,370.11	0.61	6,218.52	0.60	145.10	0.00
95% CI	6,420.32	0.61	6,267.78	0.60	159.03	0.00
2D TOF MRA only:						
mean	6,395.80	0.61	6,601.49	0.58	–205.69	0.02
5% CI	6,370.78	0.61	6,578.03	0.58	–212.62	0.02
95% CI	6,420.82	0.61	6,624.94	0.58	–198.75	0.02
SROC, 2D TOF MRA, $Q^* = 0.92$:						
mean	6,395.93	0.61	6,455.44	0.59	–59.52	0.01
5% CI	6,370.89	0.61	6,431.34	0.59	–66.53	0.01
95% CI	6,420.96	0.61	6,479.55	0.59	–52.51	0.01
Includes long-term costs of disability:						
mean	19,150.07	0.61	19,089.79	0.59	60.28	0.01
5% CI	19,047.29	0.61	18,989.95	0.59	50.53	0.01
95% CI	19,252.85	0.61	19,189.63	0.60	70.02	0.01
Excludes post hospital discharge costs:						
mean	1,400.22	0.61	1,358.41	0.59	41.81	0.01
5% CI	1,395.45	0.61	1,354.18	0.59	36.28	0.01
95% CI	1,404.98	0.61	1,362.64	0.60	47.34	0.01

TABLE 39 *Impact of capital costs and throughput: DSA versus MRA for assessment of peripheral vascular disease*

Utilisation rate (%)	DSA (£)		MRA (£)		Expected difference in cost (DSA – MRA) (£)
	Cost of DSA	Expected cost	Cost of MRA	Expected cost	
10	790	6731	1373	7575	–844
20	604	6545	748	6919	–374
30	542	6483	539	6701	–218
40	511	6452	435	6591	–140
50	492	6433	372	6526	–93
60	480	6421	331	6482	–61
70	471	6412	301	6451	–39
80	465	6405	278	6428	–22
90	459	6400	261	6409	–9
100 (base case)	455	6396	247	6395	1

Chapter 7

Analysis of the robustness of the results and sensitivity analyses

In this chapter, the robustness of the results presented in chapter 6 is analysed further. In the case of the diagnostic performance results, multiple linear regression was performed to determine if selected parameters had a significant effect on the results. The full sensitivity analyses performed as part of the decision analytic model are also discussed here.

Diagnostic performance

Carotid artery stenosis

Results of linear regression analyses

In spite of qualitative differences (*Figure 19*) between the performance using the different MRA techniques (see chapter 6), none of the variables tested in the linear regression analysis was significant at the 95% level ($p < 0.01$). The variables were: MRA technique, inclusion of asymptomatic patients; the possibility of test or diagnostic review bias; the possibility of verification bias; and the possibility of withdrawal bias. The execution of these studies was good with respect to avoiding the risk of verification bias and withdrawal bias, since only four of the 21 studies in the regression analysis had a risk of verification bias and seven had a risk of withdrawal bias. However, 11 of the 21 studies had the potential for distorted results from failing to ensure that blinding was in place to prevent test review or diagnostic review bias.

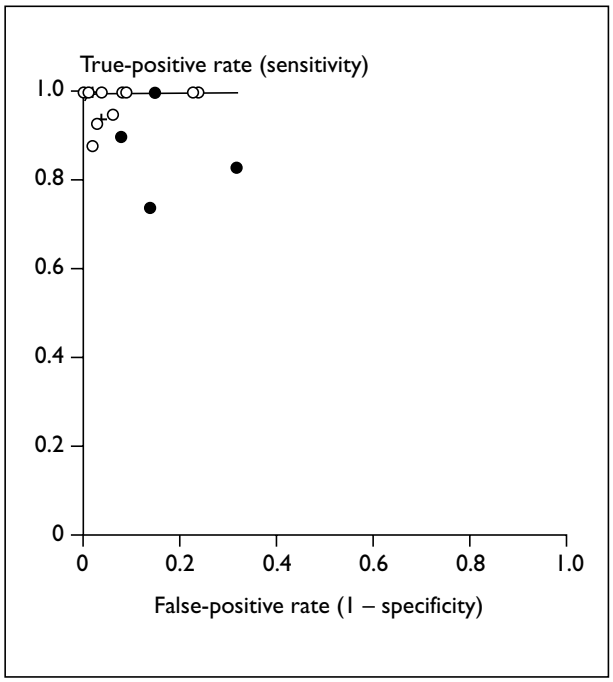

FIGURE 19 *Carotid artery stenosis: SROC curve for 2D TOF MRA, 3D TOF MRA and contrast-enhanced MRA, 0–69% or 100% versus 70–99% (number of studies included = 21). Linear regression analysis showed no significant difference between the SROC curves for the three groups; two points coincide at (0.01, 1) and two at (0, 1) (+, Contrast enhanced; ●, 3D TOF; ○, 2D TOF)*

The second analysis, which was performed on the 2D TOF 70–99% results, showed no significant difference between results published in 1994 or before, and those published from 1995 onwards.

Funnel plot

The funnel plot (*Figure 20*) has a symmetrical funnel-shaped distribution of points, which suggests that publication bias is unlikely to be present. It is notable that all but one of the studies were small.

Peripheral vascular disease

Results of linear regression analyses

In spite of qualitative differences between the performance of 2D TOF and contrast-enhanced techniques (*Figure 21*), none of the variables tested in the linear regression analysis was significant at the 95% level ($p < 0.01$). The execution of these studies was generally good, with only four of the 16 studies in the regression analysis failing to avoid the risk of diagnostic or test review bias. For verification bias and withdrawal bias, the corresponding numbers were three and two.

The second analysis, which was performed on the 2D TOF 50–100% results, showed no significant difference between results for vessels above the knee and vessels below the knee (*Figure 22*).

Funnel plot

The funnel plot (*Figure 23*) has a symmetrical funnel-shaped distribution of points, which suggests that publication bias is unlikely to be present. As for carotid artery disease, all but one of the studies were small.

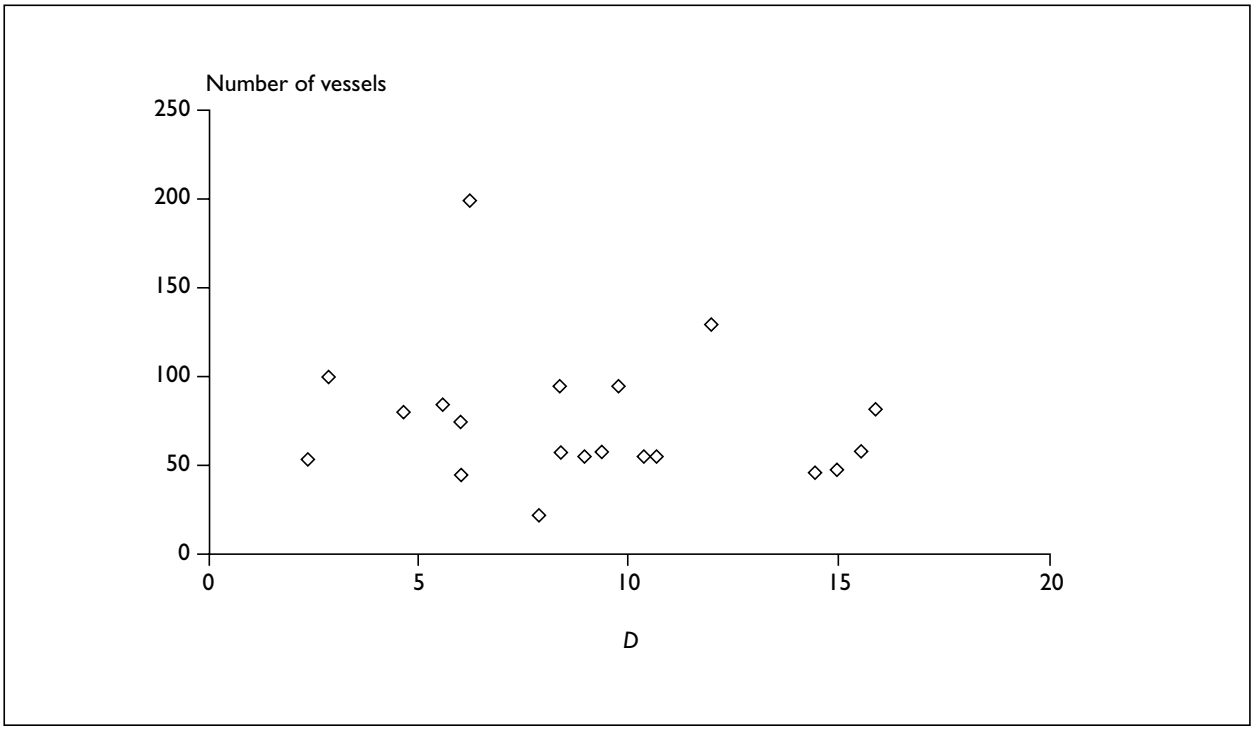

FIGURE 20 *Funnel plot of* D = *ln(diagnostic odds ratio) versus number of vessels for the 70–99% carotid artery stenosis studies (number of studies included = 21)*

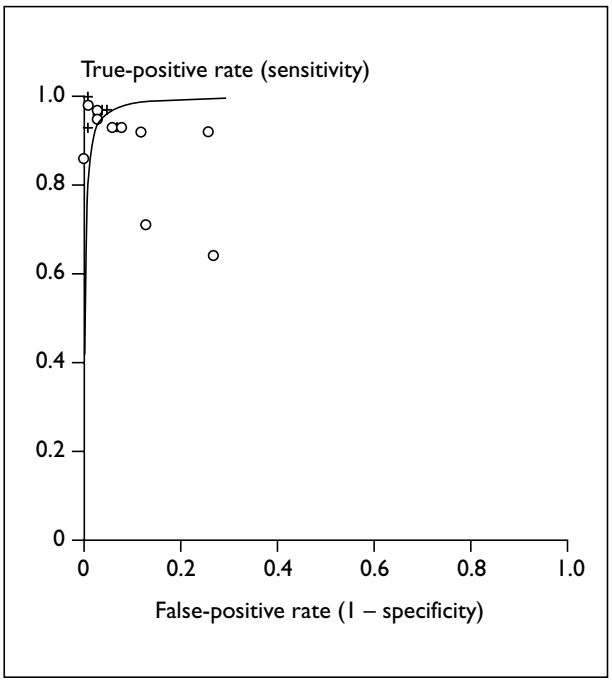

FIGURE 21 *Peripheral vascular disease: SROC curve for 2D TOF MRA (number of studies included = 10) and contrast-enhanced MRA (number of studies included = 5), 0–49% versus 50–100%. Linear regression analysis showed no significant difference between the SROC curves for the two groups (+, Contrast enhanced; ○, 2D TOF)*

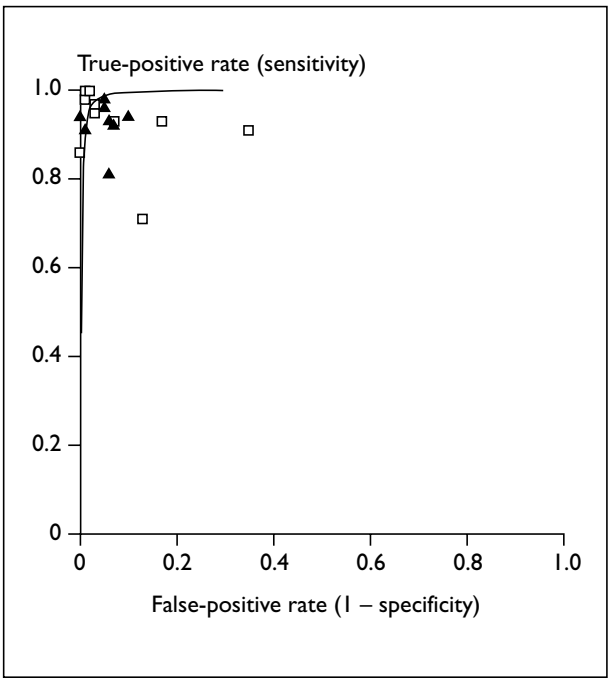

FIGURE 22 *Peripheral vascular disease: SROC curve for 2D TOF MRA, 0–49% versus 50–100%. Results for above-knee vessels (number of studies included = 11) versus results for below-knee vessels (number of studies included = 8). Linear regression analysis showed no significant difference between the SROC curves for the two groups (□, Above knee vessels; ▲, below knee vessels)*

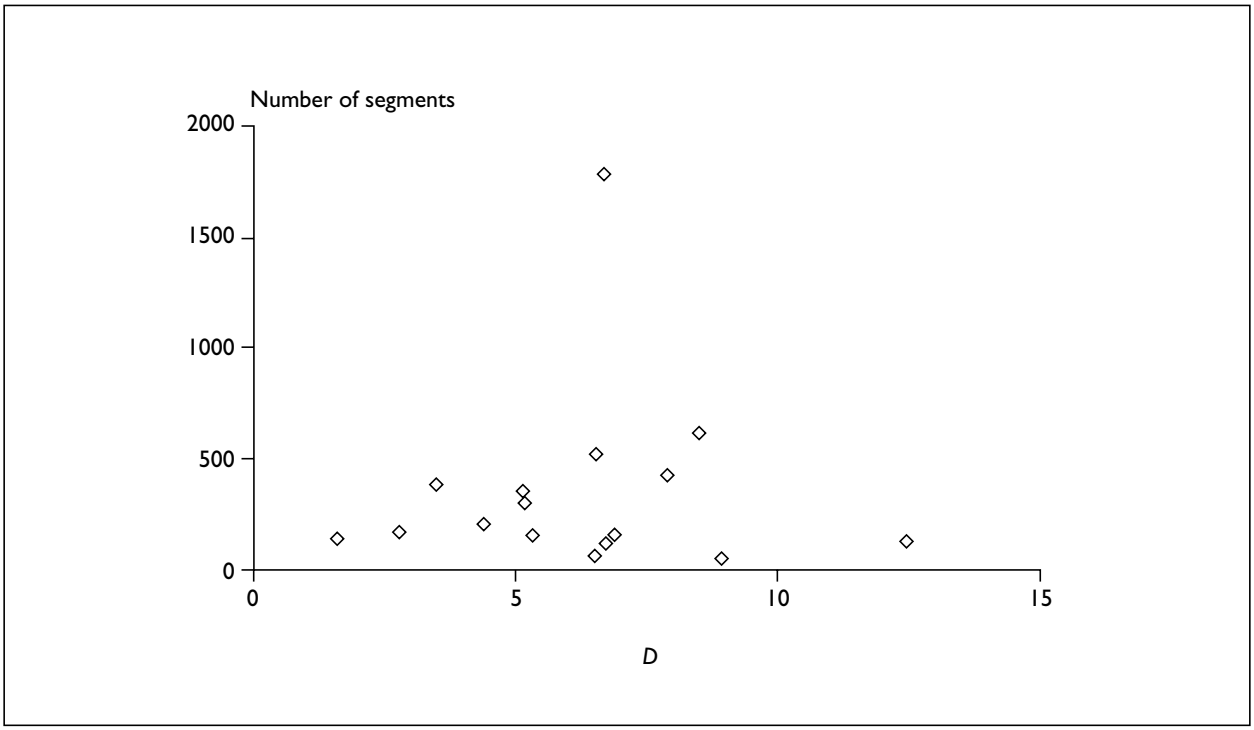

FIGURE 23 *Funnel plot of D = ln(diagnostic odds ratio) versus the number of segments for the 50–100% peripheral vascular disease studies (number of studies included = 16)*

Decision analytic model: results of sensitivity analyses

Carotid artery stenosis

The results of the base case analysis and probabilistic sensitivity analysis are given in *Table 30*. The results suggest that MRA used alone was associated with lower expected costs and similar QALYs, when compared with DSA, for most analyses. The probabilistic sensitivity analysis incorporated reported uncertainty about data included in the analysis. This is particularly important where, as here, data from several sources have been combined to estimate the value of specific variables (e.g. the probability of true- and false-positive or true- and false-negative results from MRA or DSA). However, probabilistic sensitivity analysis may not adequately represent the level of uncertainty when low levels of uncertainty are reported for data obtained from either a limited number of studies or from studies conducted in atypical settings or populations (e.g. the ECST and NASCET trials of the efficacy of endarterectomy). For this reason, additional sensitivity analysis was required to test the robustness of the results by changing the data used to estimate specific variables. This approach was used to test the impact of alternative data estimates for the sensitivity and specificity of MRA, the discount rate used for outcomes and the probability of stroke or death.

All these analyses indicated (see *Table 30*) that the results were not sensitive to changes in the estimates used for the comparison of DSA and MRA performed alone.

MRA used in combination with ultrasound resulted in higher expected costs than DSA, with lower expected QALYs. MRA combined with ultrasound was also associated with a higher expected cost and a similar outcome to MRA alone. However, the sensitivity and specificity data for the combination of MRA and ultrasound were more uncertain than those for the case of MRA alone.

Additional analyses were conducted to assess the robustness of the results to changes in the capital costs of equipment. In this case DSA is only the lower cost option compared to MRA alone if the utilisation rate of the equipment is 10% or less of the full operating capacity (see *Table 31*).

Peripheral vascular disease

The results of the base case analysis and probabilistic sensitivity analysis are given in *Table 38* and suggest that the outcomes of preoperative MRA and DSA are similar and that DSA is

associated with lower expected costs. As for the analysis for carotid artery stenosis, the probabilistic sensitivity analysis incorporated reported uncertainty about data into the analysis.

Again, probabilistic sensitivity analysis may not adequately represent the level of uncertainty when low levels of uncertainty are reported for data obtained from either a limited number of studies or from studies conducted in atypical settings or populations (e.g. the trials of preoperative MRA and DSA). Additional sensitivity analysis was required to test the robustness of the results by changing the data used to estimate specific variables. This approach was used to test the impact of alternative data estimates and assumptions about the sensitivity and specificity of MRA and the time frame of the analysis. These analyses indicated that the choice between MRA and DSA depended on the equipment available for MRA. The time frame used for the analysis did not change the conclusions of the base case analysis.

Additional analyses were conducted to assess the robustness of the results to changes in the capital costs of equipment. It was found that DSA may be the lower cost option if the equipment is used at less than 100% of its full capacity (see *Table 39*).

Chapter 8
Discussion

This chapter is divided into two main sections. Firstly, methodological issues associated with the literature review and decision analytic model are covered, following which the results of the review are discussed.

Methodology

Literature review

Search strategy

The search strategy was similar to those used in previous systematic reviews of medical imaging devices.[2,41,56] We have found that a low-precision search can be very effective in this field, where searching for articles with a particular study design, such as a randomised controlled trial, is unproductive.[302] However, only 0.1% of the articles initially identified remained after our inclusion and exclusion criteria had been applied.

In this review a limited handsearch was performed to confirm that our electronic searching method was robust. An article that had not been identified electronically was found because it was indexed only under the MeSH 'ultrasound' and did not include MRA-related text words. Although this article reported a study with a small sample size, and was later excluded, we would adapt our strategy in future work to include handsearching. Experienced handsearchers are able to search a large volume of literature remarkably quickly and efficiently. Using this revised approach, the reference lists of review articles would also be searched.

There is considerable overlap between the main databases, and 56% of the initial retrievals were subsequently excluded as duplicates. However, unique retrievals were made from all sources (see *Table 4*). Although automated duplicate checking can be performed within Reference Manager, it cannot recognise duplicates where there are small differences in the title (e.g. due to hyphenation) or where the title appears in translation. At present, hand-checking must still be performed.

For carotid artery disease, once the final inclusion criteria had been applied, no references found only in EMBASE, HealthSTAR or the Index to Scientific and Technical Proceedings remained. Of the ten articles that satisfied all the inclusion criteria, 90% came from MEDLINE and 10% from the Science Citation Index.

Similarly, for peripheral vascular disease, once the final inclusion criteria had been applied no references found only in EMBASE, HealthSTAR or the Index to Scientific and Technical Proceedings remained. Of the 20 articles that satisfied all the inclusion criteria, 90% came from MEDLINE and 10% from the Science Citation Index.

No articles satisfying all the inclusion criteria were identified by other means.

Inclusion criteria

As described in chapter 4, our inclusion criteria A–C were selected to ensure comparability of the studies and the possibility of extracting numerical results. Many would advocate that a systematic review should include conference abstracts and the grey literature, but we emphasise that this review included papers published in peer-reviewed journals only. This was because the need for comprehensive raw data means that we automatically excluded conference abstracts at an early stage and did not perform a comprehensive Internet search.

Relevance and validity

Other than those areas covered by our inclusion criteria D–H, articles were not excluded on grounds of validity, and the effect that this may have had on the results of the review is discussed later in this chapter. No significant relationship was found in the regression analysis between the results from those studies that satisfied all the carotid inclusion criteria and those that satisfied only the criteria A–D. The only variable that suggested a trend was the inclusion of asymptomatic patients, which is an example of possible patient selection bias.

Several authors have complained about poor standards of reporting in the radiological literature that can make it impossible to assess study validity.[63,303–305] A recent example[306] was initially designed as a meta-analysis, but that aim was abandoned when the poor validity of the

reported results became apparent. In this review the largest threats to study validity were: the small study groups, specifically the low numbers of positive cases included; large variations in prevalence between studies; and the risk of biases related to independence of interpretation. The possibility of blinding biases was greater for the carotid studies (11/21 in the meta-analysis) than for peripheral vascular disease (4/16 in the meta-analysis).

Data extraction

The most difficult aspect of data extraction is in determining the numbers to be put in the 2 × 2 table. A consensus approach was found to be essential. Difficulties with data extraction have been noted by other authors. In a review of MRA in peripheral vascular disease,[307] the two authors completed the 2 × 2 table differently in 8/31 studies.

Data synthesis

The SROC scatter plots of reported results show in some cases (e.g. *Figure 8* for carotid artery stenosis and *Figure 17* for peripheral vascular disease) a wide distribution of results, and a correspondingly unconvincing fitted summary curve. In the cases where there is obvious scatter, as assessed visually or as indicated by a large CI on Q^*, little emphasis should be placed on the value of Q^*. Instead, it is necessary to investigate reasons for the difference between the results. This is done later in this chapter.

The SROC method, as first described,[65] is suboptimal when several articles report 100% sensitivity or specificity (e.g. *Figures 7*, *9* and *10*). Where such values are recorded, one or more cells in the 2 × 2 contingency table will contain a value of zero, which would make it impossible to perform the logistic transformation that is needed to fit the SROC. A small adjustment is usually made to the raw data by adding 0.5 to each cell of the contingency table.[65] Where there is a large patient sample, the effect on the value of sensitivity and specificity taken forward in the SROC analysis is small, but for a sample with under 50 positive cases, the value taken forward would be 99% or under, instead of 100% (*Figure 24*).

Where there are several such points, the outcome can be a fitted SROC that, although fitting the adjusted data, does not fit the measured data well and gives an underestimated summary of performance. This is why a contingency correction of 0.01 was used in our analysis. The difference between curves fitted using different contingency adjustments is illustrated in *Figure 25*. Seventeen

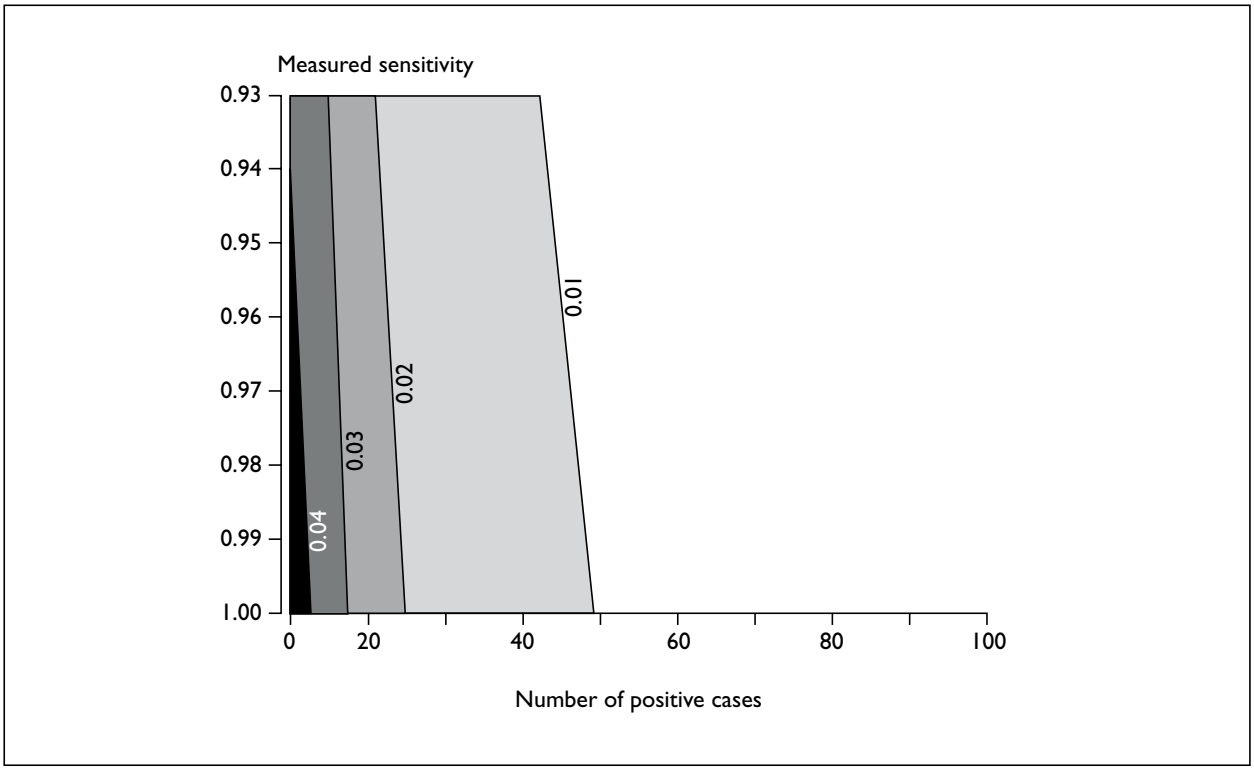

FIGURE 24 *Contingency adjustment of 0.5. The shaded areas show the difference between the measured sensitivity and the adjusted sensitivity. For example, where there are 40 positive cases, the difference is always between 0.01 and 0.02. For fewer than 10 positive cases the difference is greater than 0.03*

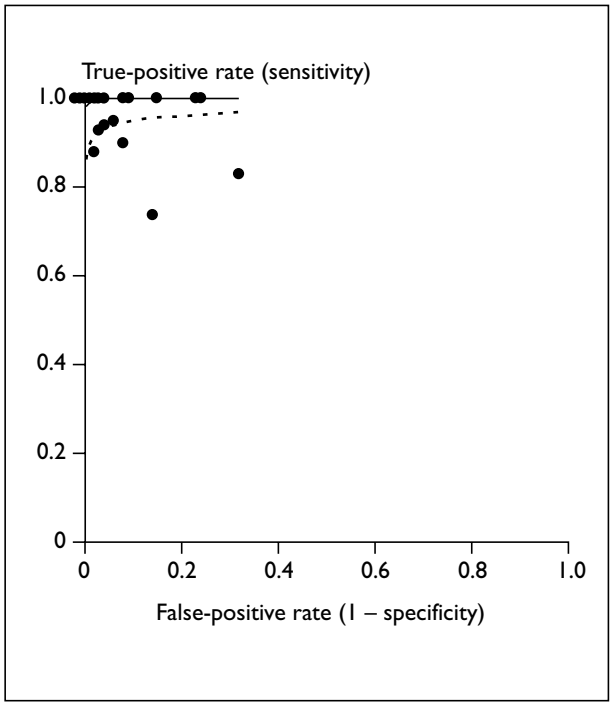

FIGURE 25 *Illustration of the effect of the size of contingency adjustment, for carotid artery stenosis, 0–69% or 100% versus 70–99% (number of studies included = 21). Points are plotted offset from one another when overlapping in false-positive rate; two points coincide at (0.01, 1) and two at (0, 1) (——, Contingency adjustment 0.01; - - - -, contingency adjustment 0.5)*

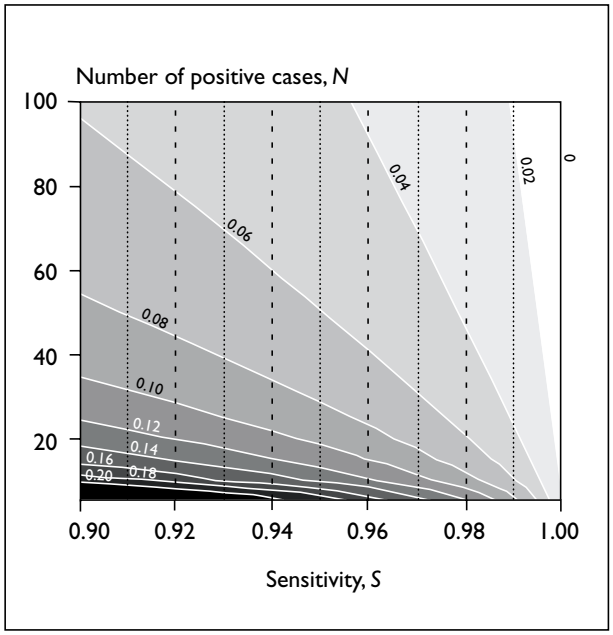

FIGURE 26 *The relationship between number of positive cases (*N*), sensitivity (*S*) and 95% CI, obtained from the expression[75] CI = ± 1.96[S(1 – S)/N]$^{1/2}$. The grey shading indicates the size of the ± 95% CI associated with combinations of* N *and* S*. For example, if it is expected that S = 0.90, the smallest number of positive cases needed to ensure that the CI is less than ± 0.10, is 35*

studies were included in this meta-analysis and all had fewer than 50 positive cases. The largest had 44, and the smallest had two.

There is a further reason to be concerned about these small studies. Each study is likely to be underpowered for the measurement of sensitivity. The relationship between the number of positive cases, sensitivity and 95% CIs is shown in *Figure 26*. It can be seen that proportionately large CIs can be expected where the number of positive cases is small.

Results from more than one observer on the same patient group were excluded from the meta-analyses. However, it is instructive to review the results in *Tables 13*, *14* and *17*, where duplicate observers are denoted by a superscript dagger (†). There are clearly some large interobserver differences, especially for the diagnosis of grades of stenosis other than occlusion. Taken together with the spread of results between studies, this demonstrates the strong operator dependence of the MRA techniques.

Decision analytic model

A decision analytic model was constructed to combine data from several sources and estimate the costs and patient outcomes associated with MRA and DSA. Probabilistic analysis was used to incorporate and quantify the level of uncertainty in the data used and the results produced. The structure and data used for the model raise a number of issues.

Model structure

The model used was static in nature, the assumption being that the value of variables does not change with time. Available evidence from the ECST and the NASCET indicates that the risk of stroke and death, key variables for the analysis, decrease over time. In addition, the change in risk differs between endarterectomy and medical management. Time is also a key factor in the success of treatment for peripheral vascular disease. For example, available evidence indicates that the patency of grafts and percutaneous transluminal angioplasty will decrease over time. Dynamic models that incorporate this change in risk (e.g. Markov models, risk models, regression models) would be conceptually more appropriate. However, these models are also complex to construct and interpret, and require a substantial amount of detailed data for each time point. The data needed to fully populate a dynamic model were not available. Expert opinion could have been used to derive assumptions to impute values

for the missing data. However, it is recognised that the use of expert data introduces unknown biases into model-based analyses and reduces the validity of the results. This is particularly important when the structure of the model is also reliant on assumptions about the direction and rate of dynamic processes (e.g. whether the risk of stroke and death decrease over time to zero, or plateau at some time point or event). One-way sensitivity analyses of each variable may not be sufficient to identify or quantify important variations in the results. Multiway sensitivity analyses are prone to investigator and expert opinion biases, in which variables and ranges of data are used to generate the scenarios used. Exhaustive multiway sensitivity analyses of all possible combinations of variables and data are not feasible in complex models such as those used here. A key criticism of modelling approaches is the quality of data used.[46,59] The impact of using a static model for key variables that may change over time was tested using sensitivity analysis to vary the 5-year risk of stroke and death in the carotid artery disease model. Lack of short- and long-term data for the peripheral vascular disease model meant that the analysis was restricted to events that occurred in the first year following diagnosis and treatment.

The structures of the models used were developed and validated by experts in radiology, and in the management of carotid artery disease and peripheral vascular disease. However, lack of data for some parts of the models meant that they had to be simplified, with some events not being included directly (e.g. the probability, costs and outcomes of transient ischaemic attack in the carotid artery model). The potential impact of these changes was explored by means of an additional sensitivity analysis.

Model data

The quality and source of the data used in models directly affects the validity and interpretation of the results for a range of settings and decision-makers. The approach taken here was, wherever possible, to minimise the use of data from expert opinion and assumptions. As is usual in these analyses, equipment list prices were used, although it is recognised that in practice list prices are very rarely paid. The calculation of capital cost per evaluation assumed a rate of 15 sessions per week for both MRA and DSA. It is likely that usage of DSA equipment is less, and this would lead to a correspondingly higher cost per evaluation for DSA. In the results of the analysis, any cost difference in favour of MRA will be increased in this situation.

Data were classified according to source and a hierarchy of the evidence applied (see chapter 3). This minimises bias, but may affect the generalisability of the results if the data are taken from studies conducted in atypical settings or populations (e.g. sensitivity and specificity of MRA and DSA). This effect was tested using additional sensitivity analysis on variables estimated from studies conducted in atypical settings or populations, and variables estimated from data with low or no reported measures of uncertainty.

Data on health state outcome following bypass surgery or angioplasty for peripheral vascular disease came from only one source.

Results of the review

Literature review: carotid artery disease

The results of the carotid meta-analyses are summarised in *Figure 27*. We know from the sensitivity analysis in chapter 7 that the differences in the SROC curves between contrast-enhanced, 3D TOF and 2D TOF MRA are not statistically significant, but this plot shows an interesting trend. Q^* is higher for the 2D TOF than for the 3D TOF methods, and the CIs increase as the diagnostic threshold is reduced. It is likely that the advantage of the larger field of view and higher spatial resolution using 3D TOF is offset by saturation occurring in the long imaged volumes. The advent of contrast enhancement was expected to redress the balance, and the good results of the small number of contrast-enhanced studies included in the review support this view.

The MRA techniques are highly accurate for identifying occlusions defined by conventional angiography, with Q^* over 99%. MRA is also effective for detecting 70–99% stenosis, where, overall for all MRA techniques, Q^* is 99% (95% CI, 98 to 100%). The evidence is not unequivocal, however, because the reports are of poor quality and there was heterogeneity between the study groups included in the review. This is discussed below. For those centres that choose to perform carotid endarterectomy on patients with 50–99% stenosis, the use of MRA to select surgical candidates is less well supported by the evidence from the literature. For all MRA techniques, the 95% CI for Q^* extends from 85% to 95%, and only two of the articles whose results were included in the meta-analysis satisfied the inclusion criteria related to validity.

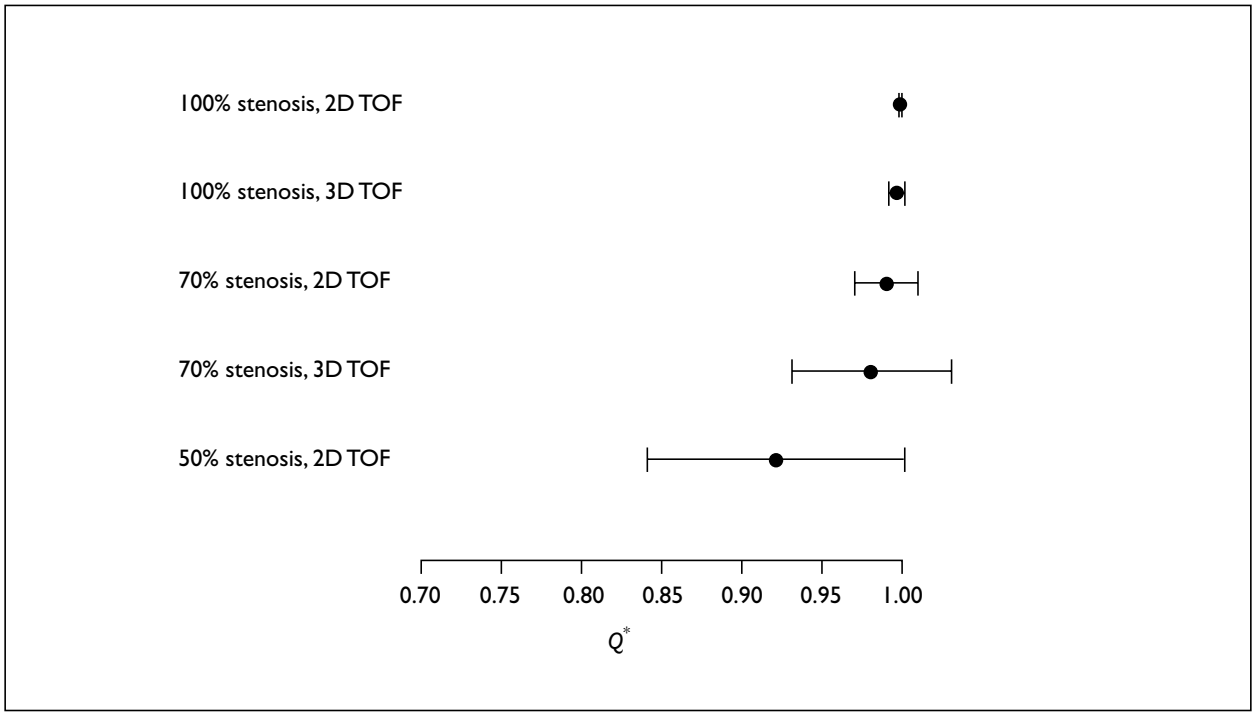

FIGURE 27 *Summary of results from the meta-analysis of the carotid artery stenosis studies*

The multiple regression approach described in chapter 7 did not explain the scatter of points that occurred for some of the analyses (e.g. in *Figures 7* and *8* for 3D TOF). The outliers on these plots are the results reported by Ozaki and co-workers[107] and Sitzer and co-workers.[105] The study by Sitzer and co-workers[105] is comparable with the other studies in most respects, except for the year of study, and it is possible that superseded techniques were used. The study by Ozaki and co-workers[107] is more recent, but had a small group of positive cases ($n = 6$) and was poorly reported, so it is hard to judge its comparability.

We did not group the studies within the technique groups by the exact protocol used. In the older articles it is possible that superseded techniques were used, but the regression analysis (for the 2D TOF results only) showed that the year of publication did not have a significant effect on the results. Similarly, it is not possible to gauge the experience or expertise of those assessing the results, and this review showed that MRA is strongly operator dependent.

The NASCET and ECST trials were very carefully controlled, since earlier studies on the benefits of carotid endarterectomy had failed to produce conclusive results. Reasons for this include poorly controlled patient selection and wide variations in perioperative complication rates. Unfortunately, the same problem is evident in the studies of MRA included in this review. There are large variations in the methods used for patient selection, which makes the validity of the results of diagnostic evaluations to select patients for carotid endarterectomy doubtful.

It is often the case that patients with suspected carotid artery disease receive an ultrasound examination, which is used as a screening test to determine if conventional angiography needs to be performed. In the articles included in this review it was not always clear if the study group comprised 'pre-screened' individuals or not. The study by Drevet and co-workers[109] is a well-reported study, and it is made clear that patients were excluded from angiography by a positive ultrasound result. The patient group was pre-screened. The prevalence in the study group was 0.21, a figure very similar to that in other articles where the patient selection procedure was less clearly described. Thus it is likely that pre-screening occurred in other studies. The prevalence is given in *Tables 10* to *16*, and it is clear that there is considerable variation between studies. If it is assumed that all patients in the studies received an ultrasound examination, then the additional cost of ultrasound applied in our model analysis may be excluded.

Reporting of the clinical symptoms of the study group was also poor, with 16 articles giving no information about patient symptoms.[94,96–99,101,103,105,113,115–117,121–124]

In order to be of value, any study of diagnostic performance must set the positive and negative test result thresholds to address a specific clinical question. In this case our question was 'Is the patient a suitable candidate for carotid endarterectomy?'. The test must be able to distinguish severely stenosed (> 70%) arteries that are suitable for carotid endarterectomy from both minimally stenosed (0–69%) and occluded arteries (100%) that are not suitable for carotid endarterectomy.[8,9] Articles retrieved for this review often failed to address the performance of MRA in these terms, even when performed after the results of the NASCET and ECST were in the public domain. Twelve articles[215–226] were excluded from the review because they did not classify operable carotid artery stenosis as 70–99% or 50–99%. Although it is essential to differentiate severely stenosed from occluded arteries when assessing a patient for surgery, seven of these articles[215–220,222] did not report the diagnostic performance of MRA for identifying occlusion.

The NASCET data show that the excess risk of stroke over 2 years for a patient in the 70–79% band is 12%, but 27% in the 90–99% band. In the future there will be a need for more focused measurement of stenosis in discrete narrow bands such as 90–99%. Future trials must take this into account and store raw data to facilitate future assessment of accuracy over any desired range.

The results of comparing MRA to duplex ultrasonography were somewhat inconclusive. Often, such comparisons between two modalities are flawed because the studies have been performed by personnel who are expert in only one of the techniques under comparison. They may perform one test with state of the art equipment and years of experience, and the other suboptimally. This does not seem to have been the case here, as the comparative studies were often undertaken by teams that had access to specialist laboratories for both investigations. The results presented in the articles certainly do not resolve the problems posed by the failure of ultrasound to provide intracranial screening,[14,15] nor do they address cost-effectiveness. The consensus appears to be that MRA and duplex ultrasonography should be used in combination, and are not in competition. As this review focused on MRA, a thorough investigation of the role of ultrasound was not performed. However, as has been indicated previously, it is now common practice to perform both ultrasound and DSA or MRA. The need for more than one examination is related to the strong inter-observer variability associated with ultrasound. Mead and co-workers[308] found that of 22 patients identified as having severe stenosis by at least one of their three observers, there was disagreement in ten that could have led to potential misreferral for endarterectomy.

One of the reasons for including this part of the review was to provide evidence to extend the model, which was based on results comparing the diagnostic performance of MRA with the gold standard of conventional angiography, to those for whom conventional angiography is unsuitable. Because they do not tolerate angiography, this patient group is missing from these evaluations, but they are also the group who might benefit most from a reliable, less invasive investigation, where the risk of stroke is removed. In the patient groups who can tolerate angiography, ultrasound and MRA used together are believed to be the most reliable option, and that result should apply equally well to those who cannot.

The ability of MRA to identify tandem lesions has not been adequately tested in the literature. The low prevalence of such lesions (one in 50 cases) means that the approach used by some of the studies in this review, where images are graded as potentially diagnostic, is probably the best way forward. Indeed, assessment in terms of haemodynamic impairment, rather than degree of stenosis, is important.[309] Given the disagreement between authors about the relevance of such lesions to the surgeon, it would appear that it might be more useful to resolve that question first, and no recommendations are made here regarding further work on identifying tandem lesions.

Only four articles considering the most recent contrast-enhanced techniques were included in the review, and only one of these satisfied all the inclusion criteria. However, the results obtained were qualitatively better than with the earlier techniques and, taken together with enthusiasm shown for the technique by radiologists and surgeons in our survey, suggest that the method will be used increasingly. MRA is an evolving technology, and there are likely to be more developments in the future. In order to assess the ability of MRA to evaluate surgical candidates, the most effective approach would be to undertake large-scale trials of the type of the NASCET and ECST, but using MRA rather than angiography to define degrees of stenosis. Such an approach would demonstrate which stenosis thresholds, as determined by MRA, produce surgical benefit, as well as determine the reliability of MRA in detecting patients suitable for surgery. However,

given the widespread penetration of MRA and the existence of the results from the earlier trials, such a trial could not ethically be undertaken. The concept of using tracker studies to evaluate fast changing technologies[310] is relevant in this area. A tracker trial would incorporate several comparisons against a standard method. Unlike the conventional trial it is designed to adapt to clinical practice by having protocols that are frequently rewritten. As new variants of MRA techniques arise they would be added to the trial, while superseded methods would be removed. Data on operator experience would also be collected, because no attempt would be made to exclude operators still at an early point on the learning curve. As this sort of trial encourages participation from users in different centres, it might also help to ensure that studies with a very small number of participants do not take place. At least 35 actually positive and actually negative cases must be present in each subgroup to reduce the CI when calculating sensitivity and specificity (see *Table 27*).

The need to make measurements over narrower bands of stenosis is associated with a need for high-resolution imaging. The residual lumen in an internal carotid artery with a 70% stenosis is only 2.4 mm, and so a 5% difference in lumen is represented by a change in residual lumen of only 0.4 mm, if we assume a normal internal carotid artery diameter of 8 mm. This suggests that isotropic resolution of approximately 0.5 mm^3 is necessary for accurate stratification. The ability to image at such high resolution will depend on implementation of faster gradients, better coil efficiency and, possibly, improved contrast agents. Such modifications are anticipated within the clinical arena in the next 2 years.

In order to demonstrate effectiveness, evidence of the impact of MRA on clinical decision-making and on patient outcome is required.[39,40] In this review we found no studies that compared MRA with conventional angiography in terms of surgical decision-making or patient outcome. Comparative studies of this sort, with patients randomised to MRA or to conventional angiography, could be used to gather evidence on the impact on decision-making.

Although the NASCET and ECST results[8,9] identified a group of patients who would benefit from carotid endarterectomy, there are still some within that group, with 70–99% stenosis, who do not need surgery. This is because the risk of stoke is related not only to the degree of stenosis, but also to the character of the plaque. It has been suggested that a thick fibrous cap is characteristic of a stable lesion, differentiating it from one that is at risk of rupture leading to thromboembolic events. We did not address the ability of MRA to characterise plaque in this review, but the MRA techniques currently used are generally not considered to be effective. Work on developing high-resolution magnetic resonance sequences that perform better is already underway,[311] and this is an important area for future research. A further area for the future is the development of non-invasive methods of determining cerebral haemodynamic compromise.[309]

Literature review: peripheral vascular disease

Although the diagnostic performance of contrast-enhanced MRA was not significantly better than for the 2D TOF techniques, the Q^* values showed a trend for contrast-enhanced MRA of improved diagnostic performance and a tighter CI. For the 0–49% versus 50–100% threshold, contrast-enhanced MRA had $Q^* = 0.98$ (95% CI, 0.95 to 1.00), while 2D TOF had $Q^* = 0.92$ (95% CI, 0.86 to 0.98). There was little scatter of points for the contrast-enhanced MRA results, but the 2D TOF results showed some variation (see *Figures 16* to *18*).

The multiple regression approach described in chapter 7 did not fully explain the scatter of points. The outliers on these plots are the results of the studies by Ho and co-workers,[131] Eklof and co-workers[130] and Mulligan and co-workers.[134] Ho and co-workers[131] studied a less severely diseased group of patients than some, with none of the patients having critical ischaemia. This may partly explain the low sensitivity, although other articles described studies on similar groups, with better results. The studies by Ho and co-workers[131] and Mulligan and co-workers[134] involved very small groups of positive cases and a low prevalence of disease. This is the most likely reason for their results differing from those of the other studies included in this review. The patient population studied by Eklof and co-workers[130] was severely diseased, with 96% suffering from critical ischaemia, and this might explain why the specificity is lower in this study than in any other for the diagnosis of occlusion. Generally, a more severely affected population results in a higher sensitivity, but this is difficult to assess here, as seven articles gave no information about patient symptoms,[93,95,132,134–136] and thus patient selection biases are highly likely. As for the carotid study groups, there is a large range of disease

prevalence, and some very small numbers of positive segments. The patients who gain the most benefit from intervention are those with critical ischaemia, but the patients studied did not necessarily fall into this group. Future studies that measure the outcome for patients following surgery must provide detailed information on the symptoms of patients.

Analysis by segment is the correct approach, as the aim of using MRA is not to diagnose on a patient or limb basis, but to localise the disease. Diagnostic performance results, especially specificity, are expected to be artefactually enhanced if normal segments are excluded from the analysis, or are low in number, as the number of false-positive results resulting from seeing a stenosis on a normal segment (because of low resolution) decreases. The results will further mislead because the diagnosis of normal, especially in the inflow vessels, is as important to the surgeon as knowledge of the location of a stenosis or occlusion. Three articles[93,138,141] excluded normal segments. Eleven articles[93,127,129,130,134–136,138–141] reported how many of the segments included in their analysis were normal, but ten did not.[37,82,92,95,128,131–133,136,137] A comparative reanalysis excluding the normal segments is not possible, because full data are available from only three studies, and one of these included no normal segments.

In addition to the variations in the number of normal segments, the studies differed considerably in the selection of vessels included. There is some debate about the optimal method to use above and below the knee. It has been reported that 2D TOF techniques may have either higher[258] or lower[312] accuracy below the knee compared with contrast-enhanced techniques; while contrast-enhanced techniques may be better above the knee.[136] Poor results from contrast-enhanced techniques below the knee could be the result of reduced distal contrast medium concentration, or interference from venous enhancement. Unfortunately, the regression analysis did not resolve this issue and showed no difference between results for above and below the knee arteries.

Use of conventional angiography as the gold standard is a problem when more vascular segments are visualised with MRA than with the gold standard reference test.[129] Some authors chose to use a measure of agreement (κ statistic) instead of sensitivity and specificity. This led to these articles being excluded from this review, although it can be argued that their approach is valid.[253,258,259,264,265] The issue of the inappropriate reference standard is discussed by Koelemay and co-workers,[313] who point out that not all multi-centre trials support the hypothesis that MRA allows visualisation of more vessels. They emphasise that the only way thoroughly to test MRA is to perform randomised trials comparing the outcomes of surgery performed following DSA and MRA.

Articles were included in the review that used both DSA and cut-film angiography as the gold standard, and this may have resulted in some heterogeneity between the results of the studies. A skilled radiologist can get excellent results using cut-film angiography, but DSA is more likely to produce satisfactory imaging of vessels below the knee where proximal disease may lead to low flow and dilution of the contrast medium.[314,315]

Since we started our review, three others on MRA and peripheral vascular disease have been published.[307,313,316] Nelemans and co-workers[316] used fewer inclusion criteria and included a thorough numerical investigation of the reasons for differences between results. They showed that contrast-enhanced MRA had a significantly higher diagnostic accuracy than 2D TOF MRA. Visser and Hunink[307] considered only contrast-enhanced MRA and compared it with duplex ultrasound. They found that contrast-enhanced MRA had a superior diagnostic performance. Koelemay and co-workers[313] had fewer inclusion criteria, but performed a detailed statistical analysis to explore the influence of quality factors. They showed that 3D contrast-enhanced MRA had a superior diagnostic performance to 2D TOF MRA. All the reviews found the same heterogeneity between studies as we did.

Contrast-enhanced techniques are already considered by some authors to be the standard magnetic resonance method[135,267,307] for the assessment of peripheral vascular disease, and the enthusiasm of those responding to our survey supports this. Proportionately more radiologists and surgeons wanted to use contrast-enhanced MRA for assessing peripheral vascular disease than for carotid artery stenosis. The lack of interest for its use in assessing carotid artery stenosis is perhaps difficult to understand, as contrast-enhanced MRA provides images that are similar to those obtained by DSA, and therefore provides a good visual assessment of the carotid arteries. However, it is possible that clinicians believe that they already have an excellent tool, as ultrasound is accurate when performed by an expert, and is cheaper and

more readily available than MRA. For peripheral vascular disease, given the potential technical problems of visualising distal calf vessels in the presence of severe proximal disease, with conventional angiography or unenhanced MRA, the potential advantages of contrast-enhanced MRA are attractive.

As was the case for the investigation of carotid artery disease, it is clear that MRA technology is evolving rapidly, and tracker trials are the most appropriate means of assessing these techniques in the future.

Decision analytic model

The data for the analysis were obtained from a range of sources. The sensitivity and specificity of MRA were estimated from the studies included in the systematic review. The problems and issues discussed in relation to the methodology need to be taken into account when assessing the relevance of the decision analysis for their setting. However, within the constraints of the data used to estimate the accuracy of MRA and DSA, the expected costs and QALYs calculated appear robust to uncertainty in the data used for the carotid artery disease analysis, but less so for the peripheral vascular disease model.

For carotid artery disease, the data for the probability of stroke and death associated with endarterectomy and medical management were taken from two tightly controlled trials, which may have overestimated the effectiveness of endarterectomy in routine practice. If the results of the analysis are to be used to guide decision-making in settings or populations where the effectiveness of endarterectomy is similar to that found in the trials, MRA appears to be the more cost-effective option. If the effectiveness of endarterectomy is thought to be lower, the analysis indicates there is little difference in costs or outcomes between the two options. It is also worth noting that the effectiveness of endarterectomy may now be better than indicated in the trials, which were performed up to 20 years ago. In this case MRA appears to be the more cost-effective option.

In peripheral vascular disease the difference in the expected costs of preoperative DSA and MRA was sensitive to the estimates of accuracy for MRA. In particular, the analysis for peripheral vascular disease suggested that there are important differences in the expected costs associated with 2D TOF and contrast-enhanced MRA, which were not found in carotid artery disease analysis. The MRA technology used did not appear to affect the patient outcomes. However, this may be due to the level of effectiveness of the subsequent treatment strategy. In the peripheral vascular disease analysis it was clear that the evidence of impact of bypass surgery and percutaneous transluminal angioplasty on long-term mobility and health status was uncertain. No attempt was made to perform subgroup analysis using separate patency results for different graft locations or types, because the wide range of uncertainty from existing trials meant that a single pooled estimate was representative and would allow a simple comparison of MRA and DSA. It is hoped that results from trials currently underway will clarify the issue. These results should be used to update our model when they are available. The model suggests that the choice of preoperative diagnostic test will depend on the type of MRA technology available and the relative effectiveness of treatment in local settings.

The number of people to be diagnosed each year affects the capital equipment costs of the various tests and the relative expected cost-effectiveness of MRA. This is particularly important if the likely utilisation rate of the equipment is less than 100% of capacity. The estimation of capital costs for this analysis was based on evaluation times of 30–40 minutes for carotid artery disease and up to 90 minutes for peripheral vascular disease. Thus, at full utilisation rates, to achieve cost-effectiveness 4500–6000 procedures are required annually for carotid artery disease and 2000 for peripheral vascular disease. Note that magnetic resonance equipment may be used for many investigations other than MRA, while conventional angiographic equipment may be used only for angiography.

The carotid disease analysis indicated higher expected costs when MRA is used in combination with ultrasound, with similar or lower outcomes. The differences in costs and outcomes are primarily due to the costs and consequences associated with conflicting results for a proportion of cases. We estimated that this was 16–18%. In the comparison with DSA, we assumed that this group of patients with conflicting evaluations (with the combined option of MRA plus ultrasound) would then have DSA, with the associated risk of stroke and subsequent costs and consequences. In the comparison of MRA alone to MRA combined with ultrasound, we assumed that patients with conflicting evaluations from the latter option would undergo additional non-invasive evaluation. This would incur additional costs, but have no impact on outcomes.

The analysis did not include the impact of the tests on patients in terms of acceptability and preferences for the procedures undergone. Nor did the analysis include risks of delays in treatment, or patient and clinician preferences associated with undergoing more than one test procedure. Data about these aspects were not available for this analysis. Research is required to identify and measure the acceptability and preferences of patients and clinicians for the diagnostic procedures. This will enable patients and healthcare providers to incorporate these aspects explicitly in the decision-making process.

Overall, the results of the economic analysis suggest that the choice of diagnostic evaluation in local settings should include consideration of:

- the numbers of people with carotid artery disease or peripheral vascular disease to be evaluated
- the relative effectiveness of subsequent treatment
- the type of MRA technology available.

General

Although we did not show any statistically significant effect on the results from study design faults, a recent article by Lijmer and co-workers,[317] which included 184 diagnostic studies, showed that such biases can have a large effect. For example, if a study used more than one reference standard, failed to blind and did not adequately describe the test, then the measured sensitivity and specificity in that study would be 84% when they should have been 70%. Failure to describe the study population was also associated with a biased test result, and this was a common failing in the articles included in this review.

There was no evidence of publication bias. Although it is encouraging that smaller studies with unexciting results are not being denied publication, it is less encouraging that really small studies, the results of which have very large CIs, are currently being published. Although there is published literature on publication bias related to therapeutic interventions, there is none that shows the validity of applying the same methods to the diagnostic literature.

As is often the case in fields where developments are constantly being introduced, the timing of this review was unsuitable for investigating the latest development. The review was begun at around the time that contrast-enhanced techniques were taken up into clinical practice, but few data exist in the literature regarding their accuracy. The literature on the method is increasing all the time, and a further, rapid, structured review, focused on contrast-enhanced techniques, would be worthwhile. It is estimated that a start date in October 2002 would allow time for sufficient work to have reached the literature.

There is already a trend suggested by the small number of results in this review that the diagnostic performance of the contrast-enhanced techniques is better than TOF methods. This improved performance may be related to a number of technical factors, including the ability to scan in the coronal plane, increased signal-to-noise ratio and increased spatial resolution, both of which can be achieved by adapting the injection rate and volume.

In general, however, TOF techniques remain in widespread use and there is a significant body of published work evaluating their diagnostic performance. Our survey showed that where users, in particular radiologists, expressed a preference, they tended to favour the most recent technology, even though the published evidence evaluating its diagnostic performance may be limited. Clinical end users, in this case vascular surgeons, were more cautious in their use of MRA, often preferring not to use it at all. They appeared to be more likely to be satisfied with the technique that is currently available to them, but we were aware that the equipment question on our questionnaire meant that some surgeons felt they could not complete it. Furthermore, these observations represent limited evidence, as they were not obtained using a rigorous survey methodology. One approach which was outside the scope of this study would be to use conjoint analysis, a method that is increasingly applied to study both patient[318,319] and clinician[320] preferences. There were no published data on the acceptability of MRA to patients and clinicians.

The effect of image processing and presentation was not investigated, primarily because insufficient information was given in the articles. It is likely that more accurate results are obtained by using both source images and maximum intensity projections, rather than the maximum intensity projections alone, and this is worthy of further investigation. Indeed, this is just one aspect of the issue of good practice.

If cost-effectiveness is to be achieved in regular clinical practice, there is a need for evidence-based practice guidelines to be established by the relevant professional bodies, together with training and accreditation schemes.

Our conclusions about cost-effectiveness are valid only for high-quality diagnostic studies. Such examinations can only be performed following training and adequate experience. If cost-effectiveness is to be achieved in regular clinical practice, there is a need for evidence-based practice guidelines to be established by the relevant professional bodies, together with training and accreditation schemes. Currently, there are guidelines governing the training requirements for radiologists wishing to specialise as interventional radiologists. In most centres, carotid arteriography is only performed by those with extensive experience of the technique (typically vascular radiologists and neuro-radiologists). However, no such training standards are imposed on those radiologists conducting vascular magnetic resonance examinations. These observations lead to the conclusion that a structured training programme should be introduced that puts in place minimum standards that must be reached by all those responsible for delivery of an MRA service. An ongoing programme of audit would be necessary to ensure that high standards were maintained in perpetuity.

Technical guidelines regarding the minimum acceptable performance of MRA equipment would also be valuable. These guidelines should be based on the findings of this and other reviews. However, given the uncertainty introduced by gaps in the evidence, it would be necessary for compilation to be performed by a small team of international experts, both clinicians and radiologists, who have extensive expertise of both the clinical focus and the ability of magnetic resonance systems to address the issues.

As has been the case in our previous reviews on medical imaging topics, the doubtful validity of the studies included in the review means that some of the conclusions must be treated cautiously. Does this mean that undertaking the review was not justifiable? This issue has recently been addressed by Alderson and Roberts[321] in an article entitled 'Should journals publish systematic reviews that find no evidence to guide practice? Examples from injury research'. They point out the benefits of admitting uncertainty, and their comments make a fitting end to this chapter:

> So the uncertainty demonstrated in systematic reviews can help clarify the options available to clinicians and patients. It can stimulate more research and better research and so help to resolve uncertainty. Uncertainty should not be hidden away as an embarrassment. We should be willing to admit that 'we don't know' so that the evidential base of healthcare can be improved for future generations.

Conclusion

In this chapter we have discussed our methodology and findings. In the next chapter the implications of the review, in terms of healthcare and future research, are predicted.

Chapter 9
Conclusions

Implications of the review for healthcare

In carotid artery disease the 2D TOF and 3D TOF MRA techniques are accurate for identifying both occlusions and 70–99% stenoses, as defined by conventional angiography. The evidence does not support the use of these techniques for identifying 50–99% stenoses.

If the overall utilisation rate for an MRI system is greater than 10%, then MRA is associated with a lower expected cost than DSA and is the cost-effective option for the investigation of carotid artery disease.

In peripheral vascular disease 2D TOF and contrast-enhanced MRA techniques are accurate for identifying occlusions and 50–100% stenoses, as defined by conventional angiography.

DSA is associated with lower expected costs than MRA for all rates of utilisation less than 100% and is the cost-effective option for the investigation of peripheral vascular disease. However, if both DSA and MRA are already available in the local setting, MRA is associated with a lower expected cost than DSA, especially if contrast-enhanced MRA is available.

The choice of method for investigating peripheral vascular disease is influenced by the treatment effectiveness achieved by a centre, and it is necessary for such data to be gathered for an informed decision to be made.

Care should be taken to ensure that the use of MRA is considered when development bids for magnetic resonance equipment are under preparation.

The conclusions about cost-effectiveness are valid only for high-quality diagnostic studies. Such examinations can only be performed following training and adequate experience. There is, consequently, a case for guidelines for the performance of and interpretation of MRA, and for training and accreditation schemes to be established by the relevant professional bodies.

Recommendations for further research

- The lack of evidence from high-quality trials and on the newer and evolving techniques, suggests the need to establish a multicentre tracker study to determine the accuracy of MRA, duplex ultrasound and CT angiography (singly or in combination) for the investigation of carotid artery disease. Data from this trial should be collected and stored in a manner that will allow sensitivity and specificity to be determined over narrow bands of stenosis values. The trial must ensure that comparisons are performed of the proportions of patients who are misdiagnosed and the outcomes of health status and health-related quality of life. An evaluation of cost-effectiveness is essential.
- The lack of evidence from high-quality trials and on the newer and evolving techniques suggests the need to establish a multicentre tracker study to determine the accuracy of contrast-enhanced MRA, duplex ultrasound and CT angiography (singly or in combination) for the investigation of peripheral vascular disease. Data from this trial should be collected and stored in a manner that will allow analysis into predefined arterial segments. The trial must ensure that comparisons are performed of the proportions of patients who are misdiagnosed and the outcomes of health status and health-related quality of life. An evaluation of cost-effectiveness is essential.
- Support for data from primary studies to be held on webservers is recommended, as it would facilitate future modelling activity.
- The lack of evidence about contrast-enhanced MRA supports the need for a rapid, structured review focused on contrast-enhanced MRA. This might commence around October 2002.
- As more papers are excluded from meta-analyses than is desirable, measures to reduce the number of exclusions are needed. It is suggested that one of the NHS-supported HTA Centres coordinates the compilation of general guidelines for designing and presenting trials of diagnostic and imaging technologies. Parties to involve might include the Cochrane Screening and Diagnostic Tests Methods Group, authors of systematic reviews and meta-analyses on

diagnostic topics, researchers supported by the NHS to perform primary studies in these fields, methodological experts and journal editors. Subject-specific clinical expertise may also be appropriate, in this case from the Cochrane Stoke and Peripheral Vascular Disease Groups. Key reasons for exclusion of studies from this review were the lack of a gold standard comparison, inadequate information on the patients studied and insufficient raw data.

- It is unclear whether the accepted work on publication bias applies to diagnostic and screening studies, and a methodological investigation specifically focused on such literature is indicated.
- The results from modelling show an apparent lack of differences in outcome between DSA and MRA, suggesting that the choice between them will depend on the equipment available and the preferences of the clinician and patient. Studies on patient preferences for the diagnostic process and expected impact on their health status and health-related quality of life are indicated.
- Monitoring of expert opinion is indicated, to ensure that trials of new non-invasive MRA techniques are implemented in a timely way. Methods for assessing carotid plaque morphology and the detection of cerebral haemodynamic compromise are examples.
- Updating of the peripheral vascular disease model when the results of the NHS-supported multicentre trial Multi-centre Randomised Controlled Trial of the Cost-effectiveness of Infra-inguinal Percutaneous Transluminal Angioplasty versus Reconstructive Surgery for Severe Limb Ischaemia are available in 2005.

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Appendix 1

Search strategies

Abbreviations and commands used in electronic search strategies are given in *Table 40*.

TABLE 40 *Commands and abbreviations used in electronic search strategies*[*]

Abbreviation or command	Definition
$	Truncation symbol for MEDLINE and EMBASE
*	Truncation symbol for BIDS, Cochrane, Inside and Reference Manager
adj	Adjacent command for MEDLINE and EMBASE
#	Wild word command for BIDS
exp	Explode command for MEDLINE and EMBASE
ti	Title command for MEDLINE and EMBASE
ab	Abstract command for MEDLINE and EMBASE
hw	Headword command for MEDLINE and EMBASE (i.e. a single word anywhere in an MeSH term)
tw	Text word command for MEDLINE and EMBASE
tka	Title, Keyword, Abstract command for BIDS
PY	Publication year
, + –	BIDS Boolean commands OR, AND, NOT, respectively
"-"	The BIDS search engine does not ignore the hyphen. Hyphenated words must be separately specified, and enclosed in quotation marks to avoid confusion with the use of the hyphen for the Boolean NOT command. Hyphens are ignored in MEDLINE and EMBASE searches

[*] *The OVID search interface was used in this review to access MEDLINE and EMBASE. At the time of our searches, the Science Citation Index and Index to Scientific and Technical Proceedings (provided by the Institute of Scientific Information) could be accessed from the BIDS website. The BIDS search terms described above applied to the interface used on this website*

MRA

MEDLINE and EMBASE

1. Magnetic resonance angiography/
2. mra.tw.
3. ((MR or (magnet$ adj3 resona$)) adj3 angiograph$).tw.
4. 1 or 2 or 3

HealthSTAR

1. mra
2. mr # angiograph?
3. mri # angiograph?
4. magnetic resonance # angiograph?
5. CT D magnetic resonance angiography
6. CT D endarterectomy
7. CT D angioplasty
8. CT D arteriosclerosis
9. CT D peripheral vascular disease
10. CT D angiography
11. CT D magnetic resonance imaging
12. 1 or 2 or 3 or 4 or 5
13. 6 or 7 or 8 or 9
14. (10 and 11 and 13) or 12

BIDS–Science Citation Index and BIDS–Index to Scientific and Technical Proceedings (ISTP)

1. Magnetic resonance angiograph*.tka
2. Magnetic resonance # angiograph*.tka
3. Magnetic resonance # # angiograph*.tka
4. Magnetic resonance # # # angiograph*.tka
5. MRA.tka
6. MR angiograph*.tka
7. "MR-angiography".tka
8. "MR-angiographic".tka
9. MR # angiograph*.tka
10. MR # # angiograph*.tka
11. MR # # #angiograph*.tka
12. 1,2,3,4,5,6,7,8,9,10,11

Inside, Online Computer Library Centre

"magnetic resonance angiograph*" OR "mr angiograph*" OR "mra"

Outcomes

The following general strategies were adapted for use in the individual databases:

1. "Carotid-Stenosis"/ all subheadings
2. carotid stenosis
3. carotid artery stenosis
4. "Carotid-Stenosis"/ drug-therapy
5. explode "Endarterectomy"/ all subheadings
6. "Angioplasty-Transluminal,-Percutaneous"/ all subheadings
7. explode "Heparin"/ all subheadings
8. "Aspirin"/ all subheadings
9. explode "Anticoagulants"/ all subheadings
10. endarterectomy
11. pta or percutaneous transluminal angioplasty
12. medical management or medical therapy or medical treatment
13. anticoagul*
14. tia or transient ischaemic attack* or transient ischemic attack*
15. cranial nerve injur*
16. myocardial infarction*
17. neck haematoma* or neck hematoma*
18. "Ischemic-Attack-Transient"/ all subheadings
19. explode "Hospitalization"/ all subheadings
20. "Myocardial-Infarction"/ all subheadings
21. length of stay
22. patient readmission
23. hospitalisation or hospitalization
24. hospital near (admission or readmission or stay or length or cost*)
25. stroke* in ti,ab
26. #1 or #2 or #3
27. #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
28. #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
29. #26 and #27 and #28
30. #29 and (PY >= "1990")

1. "Peripheral-Vascular-Diseases"/ all subheadings
2. peripheral vascular disease*
3. peripheral vascular occlusive disease*
4. peripheral artery disease*
5. peripheral arterial disease*
6. ischem*
7. ischaem*
8. leg
9. legs
10. limb
11. limbs
12. extremit*
13. critical
14. "intermittent-claudication"/ all subheadings
15. "Angioplasty-Transluminal,-Percutaneous"/ all subheadings
16. pta or percutaneous transluminal
17. angioplasty
18. "vascular surgery"/ all subheadings
19. reconstruction
20. bypass
21. revascularisation
22. medical management or medical therapy or medical treatment
23. "fibrinolytic-therapy"/ all subheadings
24. streptokinase
25. urokinase
26. "tissue plasminogen-activator"/ all subheadings
27. explode "hospitalization"/ all subheadings
28. length of stay
29. patient readmission
30. hospitalisation or hospitalization
31. hospital near (admission or readmission or stay or length or cost*)
32. #1 or #2 or #3 or #4 or #5
33. #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
34. #15 or #16 or #17 or #18 or #19 or #20 or #21
35. #22 or #23 or #24 or #25 or #26
36. #27 or #28 or #29 or #30 or #31
37. #32 or #33
38. #34 or #35
39. #35 and #36 and #37 and #38

Costs

The following general strategy was adapted for use in the individual databases:

1. "Carotid-Stenosis"/ all subheadings
2. carotid stenosis
3. carotid artery stenosis
4. #1 or #2 or #3
5. "Peripheral-Vascular-Diseases"/ all subheadings
6. peripheral vascular disease*
7. peripheral vascular occlusive disease*
8. peripheral artery disease*
9. peripheral arterial disease*
10. #5 or #6 or #7 or #8 or #9

11. explode "Costs-and-Cost-Analysis"/ all subheadings
12. cost* or econom* or resource* or expenditure or burden
13. #11 or #12
14. #4 and #13
15. #10 and #13
16. #14 and (PY >= "1990")
17. #15 and (PY >= "1990")

Appendix 2

Questionnaire

5 January 2000

Dear

The cost-effectiveness of magnetic resonance angiography: carotid artery stenosis and peripheral vascular disease

We have been commissioned by the UK National Health Service (NHS) R&D Programme to undertake the above review (reference 97/13). Systematic literature reviews are now a key part of the NHS R&D strategy, and the evidence-based results will influence future clinical practice in the UK.

We should be most grateful if you would complete and return the short questionnaire below. Your responses will help to ensure that our study is relevant to current clinical practice. Thank you very much for taking the time to respond.

Yours sincerely

Mr MJ Gough, Consultant Vascular Surgeon

Dr JFM Meaney, Consultant Radiologist

The standard MR protocol used in my hospital to assess the degree of carotid artery stenosis in patients presenting with TIA/stroke is:

☐ 2D time of flight (TOF)
☐ 3D time of flight (TOF)
☐ Contrast-enhanced MR techniques
☐ MRA not used

If all methods were equally available, my method of choice would be:

☐ 2D time of flight (TOF)
☐ 3D time of flight (TOF)
☐ Contrast-enhanced MR techniques
☐ Would not use MRA

The standard MR protocol used in my hospital to assess peripheral vascular disease prior to therapy is:

☐ 2D time of flight (TOF)
☐ 3D time of flight (TOF)
☐ Contrast-enhanced MR techniques
☐ MRA not used

If all methods were equally available, my method of choice would be:

☐ 2D time of flight (TOF)
☐ 3D time of flight (TOF)
☐ Contrast-enhanced MR techniques
☐ Would not use MRA

The following are available in my hospital:
☐ 2D TOF ☐ 3D TOF ☐ Contrast-enhanced MRA

Field strength/s of MR systems/s in my hospital:
☐ 0.5 T ☐ 1.0 T ☐ 1.5 T ☐ Other, please state

Name and address of hospital/institution:

Please return this sheet by fax to

or post to:

Appendix 3

Checklists

Study design: checklist for diagnostic performance studies

1.	Where was the study conducted?	_____
2.	Time period of the study?	_____
3.	Randomised?	Y/N/NR
4.	Observational?	Y/N/NR
5.	Prospective?	Y/N/NR
6.	Retrospective?	Y/N/NR
7.	Patients undergoing selective contrast angiography examination	_____ %
8.	Patients undergoing MRA examination	_____ %
9.	Patients undergoing ultrasound examination	_____ %
10.	Patients unable to tolerate MRA	_____ %
11.	Vessels excluded from analysis due to failure of DSA	_____ %
12.	Vessels excluded from analysis due to failure of MRA	_____ %
13.	Vessels excluded from analysis due to failure of ultrasound	_____ %
14.	Order in which the examinations were performed	_____
15.	Average delay between examinations	_____
16.	Vessels excluded from analysis due to delay	_____ %
17.	Degrees of stenosis defined?	Y/N
18.	NASCET criteria used? (Carotid only)	Y/N
19.	ESCT criteria used? (Carotid only)	Y/N
20.	Number of readers interpreting examinations:	
	(a) DSA	_____
	(b) MRA	_____
	(c) Ultrasound	_____

Carotid artery stenosis: clinical checklist for diagnostic performance studies

1.	Total number of patients	_____
2.	Total number of vessels studied	_____
3.	Male patients	_____ %
4.	Age range	_____ years
5.	Symptomatic?	_____ %
6.	Cardiac symptoms?	_____ %
7.	Carotid bruits?	_____ %
8.	TIA?	_____ %
9.	Amaurosis fugax?	_____ %
10.	Unilateral hemispheric event?	_____ %
11.	Stroke?	_____ %
12.	Previous endarterectomy?	_____ %
13.	Diabetic?	_____ %
14.	Hypertensive?	_____ %
15.	Proceeded to endarterectomy?	_____ %
16.	Time from most recent symptoms	_____

Peripheral vascular disease: clinical checklist for diagnostic performance studies

1.	Total number of patients	_____
2.	Total number of vessels studied	_____
3.	Male patients	_____ %
4.	Age range	_____ years
5.	Symptomatic	_____ %
6.	Claudication	_____ %
7.	Ischaemia/rest pain	_____ %
8.	Tissue loss	_____ %
9.	Fontaine classification	_____
10.	Previous bypass	_____ %
11.	Previous angioplasty	_____ %
12.	Diabetic	_____ %
13.	Proceeded to angioplasty	_____ %
14.	Proceeded to bypass	_____ %
15.	Proceeded to bypass + toe amputation	_____ %
16.	Proceeded to toe amputation	_____ %
17.	Proceeded to below-knee amputation	_____ %
18.	Proceeded to above-knee amputation	_____ %
19.	No intervention:	_____ %
	(a) No intervention possible	_____ %
	(b) Intervention not clinically justified	_____ %
	(c) Palliative treatment	_____ %
20.	Which vessels studied?	_____

Carotid artery stenosis and peripheral vascular disease: MRA technical checklist for diagnostic performance studies

Article details

Title:

Main author:

Centre:

Year:

Journal:

MRA technology

1.	MR manufacturer and model	_____
2.	Field strength:	_____ T
3.	Coil type (e.g. head, neck)	_____
4.	Moving table?	Y/N

MRA parameters

5.	Pulse sequence type	_____
6.	Repetition time (TR)	_____ ms
7.	Echo time (TE)	_____ ms
8.	Flip angle	_____°
9.	Slice thickness:	
	(a) Actual	_____ mm
	(b) Interpolated	_____ mm
10.	Number of slices	_____
11.	Field of view	_____ × _____ mm
12.	Matrix:	
	(a) Scan	_____ × _____ mm
	(b) Reconstruction	_____ × _____ mm
13.	Plane	sagittal transverse coronal
14.	Acquisition time	_____ s
15.	Examination time	_____ min

16. Contrast enhanced? Y/N

    If yes:
    - (a) Contrast agent _____
    - (b) Dose _____
    - (c) Rate _____
    - (d) Scan timing method _____
    - (e) Subtraction? Y/N
    - (f) Other _____

17. Breath hold? Y/N
18. Cardiac gated? Y/N
19. Type of visualisation _____
20. TONE? Y/N

Bias checklist

This checklist is eight pages long.

Article details

Title:

Main author:

Centre:

Year:

Journal:

Patient selection biases

A. Referral bias

A1. Is the establishment(s) where the study was undertaken stated?

[ ] **Yes** The establishment(s) is stated in the text or the establishment(s) is identifiable from the authors' correspondence addresses. The establishment is the place of origin of the study, such as a university hospital or a cancer institute.

[ ] **No** It is not stated and it is unclear from which author's establishment the study was conducted.

A2. Is the establishment from where the patients were referred stated?

[ ] **Yes** It is clearly stated in the text. For example, referred from local general practices.

[ ] **No** It is not stated.

A3. Is the access to the establishment described?

[ ] **Yes** It is stated that the establishment is open access, referral based, public or private, etc.

[ ] **No** No information.

B. Patient filtering bias

B1. Are patients excluded from the study before receiving the diagnostic test?

[ ] **Yes** It is clear that not all patients referred enter the study.

[ ] **No** It is stated that all patients referred to the centre receive the diagnostic test, e.g. consecutive.

[ ] **?** Insufficient or unclear information.

B2. Are specific eligibility criteria stated for those included/excluded?

[ ] **Yes** Criteria are either reported for all those who do receive the test or those who do not, and the total number of patients referred is given as well as the number included/excluded.

[ ] **No** Criteria or numbers are not reported.

B3. Is co-intervention bias present?

[ ] **Yes** A selective proportion of the study group have received additional interventions to that being studied. Such interventions include any prior surgery, treatment or tests which are likely to influence the final test performance. This is also known as 'treatment paradox'.

[ ] **No** It is stated that all or none of the study group received additional interventions.

[ ] **?** Insufficient information.

B4. Is co-intervention bias avoided via the eligibility criteria?

[ ] **Yes** It is clearly stated that patients are excluded if they have had additional interventions.

[ ] **No** It is clear that patients were included despite co-interventions.

[ ] **?** Insufficient information.

C. Patient cohort bias

C1. Are the study groups' clinical details described?

[ ] **Yes** Severity or chronicity of symptoms is reported along with sex ratio, age range and mean age of both the initial referral group and those receiving a final diagnosis.

[ ] **No** Neither severity or chronicity, or less than three of the demographics, are reported. Or demographics are not given for both the initial referral group and those receiving a final diagnosis.

C2. Are the study groups' pathologic details described?

[ ] **Yes** Type and location of disease is reported for either the initial referral group or those receiving a final diagnosis.

[ ] **No** None or only one of the above are reported.

C3. Are any co-morbid conditions described for the study group?

[ ] **Yes** *Any* co-morbid conditions, or absence of conditions are reported for *any* patients. A co-morbid condition is any illness or parameter attributable to the condition being diagnosed. For example, when diagnosing liver cancer attributable co-morbid conditions can include secondary cancers or cirrhosis.

[ ] **No** No information regarding co-morbid conditions is reported.

[ ] **?** Additional conditions are reported, but their significance or connection with the condition being diagnosed is unclear.

Biases associated with application of the gold standard

Before proceeding, the definition of a gold standard needs to be clarified with regard to the diagnostic speciality being considered. For diagnostic accuracy to be calculated the outcome of the diagnostic test being investigated needs to be compared to the 'true diagnosis'. This 'true diagnosis', or comparator, can be obtained by a variety of methods depending on the diagnostic speciality, and this is known as the gold standard. As an expert in your field please define the acceptable gold standards here.

.....

.....

D1. Is verification bias present?

[ ] **Yes** Not all of the patients whom have received the diagnostic test go on to receive the gold standard (as defined above). There are many reasons for patients not receiving the gold standard, for example safety, cost, or patient preference.

[ ] **No** All patients receive the gold standard test or a correction is performed by the authors.

[ ] **?** Insufficient or unclear information.

D2. Is work-up bias present?

[ ] **Yes** The result of the diagnostic test is used to decide who receives the gold standard (as defined above).

[ ] **No** It is clear that the diagnostic test is not used to decide, or a correction is performed by the authors.

[ ] **?** Insufficient or unclear information.

D3. Is incorporation bias present?

[ ] **Yes** Patients receive verification of the 'true diagnosis' via the diagnostic test under evaluation. This usually occurs when the diagnostic test under investigation is used to 'follow up' the patients.

[ ] **No** The diagnostic test is not used as verification.

[ ] **?** Insufficient information.

Biases due to the measurement of results

E. Disease progression bias

Before answering this question an acceptable number of days, *x*, between the diagnostic test and verification with the gold standard *in your speciality* needs to be defined. It depends on the aetiology and understanding of the condition under evaluation. It is important as delay between testing and verifying the condition could allow sufficient change in the condition to occur.

If you feel you can estimate a reasonable time period, please state it here: *x* = ... days

E1. Is disease progression bias present for the test under evaluation?

[ ] **Yes** The time between the diagnostic test and verification with the gold standard is greater than or equal to *x* days (as defined above).

[ ] **No** The time is less than *x* days (as defined above).

[ ] **?** No information is given.

[ ] The information is supplied but you are unaware of the significance. The delay is reported as .....

F. Withdrawal bias

F1. Are results reported for all patients who received verification?

[ ] **Yes** Results are clearly reported for all patients who received verification with the gold standard test.

[ ] **No** Results are missing or selective results are reported.

[ ] **?** Insufficient information.

G. Observer variability bias

G1. Is there a single observer of the diagnostic test under evaluation?

[ ] **Yes** All images from the test under evaluation are interpreted by one person.

[ ] **No** More than one interpreter.

[ ] **?** Insufficient information.

G2. If no, are results reported separately for each observer?

[ ] **Yes** All results are reported independently for all observers.

[ ] **No** Not all results are reported separately.

G3. Are the diagnostic test results taken from a consensus decision?

[ ] **Yes** It is clearly stated that all or some of the test results are a consensus decision.

[ ] **No** It is clear that it was not a consensus decision.

[ ] **?** Insufficient information.

G4. Is any attempt made to assess interobserver variability?

[ ] **Yes** Data are reported statistically, with the kappa statistic, or illustrated in a ROC curve for interobserver variation.

[ ] **No** No data are provided.

[ ] **?** Insufficient information.

G5. Is any attempt made to assess intra-observer variability?

[ ] **Yes** Data are reported statistically, with the kappa statistic, or illustrated in a ROC curve for intra-observer variation.

[ ] **No** No data is provided.

[ ] **?** Insufficient information.

Independence of interpretation biases

H1. Is diagnostic review bias present?

[ ] **Yes** Observers are aware of the results of the diagnostic test when interpreting the gold standard.

[ ] **No** It is stated that observers are blinded or unaware of the diagnostic test results.

[ ] **?** Insufficient information.

H2. Is test review bias present?

[ ] **Yes** Observers are aware of the results of the gold standard when interpreting the diagnostic test.

[ ] **No** It is stated that the observers are blinded or unaware of the gold standard results.

[ ] **?** Insufficient information.

H3. Is comparator review bias present?

[ ] **Yes** More than one diagnostic test is compared to the gold standard and observers are aware of one test's results when interpreting the other test.

[ ] **No** It is stated that all the diagnostic tests were read independently or blind to the other tests. Or only one diagnostic test is used.

[ ] **?** Insufficient information.

H4. Is clinical review bias present?

[ ] **Yes** It is stated that the observers are aware of the clinical details and history of the patients.

[ ] **No** It is stated that the observers are blinded to the clinical data.

[ ] **?** Insufficient information.

Appendix 4

Details of studies included in the review

Eight tables (*Tables 41* to *48*) are presented here. The articles are in the same order as they appear in chapter 4.

TABLE 41 *Carotid artery stenosis: articles satisfying all the inclusion criteria A–H*

	Scarabino, 1999[96]	**Chiesa, 1993**[97]	**Link, 1996**[94]	**Magarelli, 1998**[98]	**Scarabino, 1998**[99]	**Uehara, 1995**[100]	**Dadachanji, 1995**[101]	**Huston, 1993**[102]	**Laster, 1993**[103]	**White, 1994**[104]
Time period	May–Sep. 1997	Jun. 1991–Jun. 1992	NR	NR	Jan.–Apr. 1996	Apr. 1992–Aug. 1994	NR	NR	NR	NR
Magnetic resonance technology	Contrast enhanced, 1.5 T	3D TOF, 1.5 T	3D TOF, 1.5 T	3D TOF, 1.5 T	3D TOF, 3D PC, 2D TOF, 1.5 T	3D TOF, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T
TR/TE/α	10/min./60	NR	80/6/25	50/8/20	50/8/20, 25/9/20, 46/9/60	40/10/20	45/min./60	45/8.7/60	50/10.5/50 or 45/8.7/60	40/8.7/70
Imaging plane	Coronal	Axial	Sagittal	Axial	Axial	Axial	Axial	Axial	Axial	Axial
NASCET method of measuring stenosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No. of patients	23	63	40	20	64	44	20	52	101	70
No. of vessels	46	126	80	40	128	81	40	98	202	120
% Male	61	65	60	60	NR	73	NR	70	NR	55
Age range (years)	63–73	54–79	39–76	Mean 65	NR	33–79	38–75	42–82	37–83	44–89
% Symptomatic	100	100	100	100	100	100	100	100	100	100
Further details on symptoms given in article	No	No	No	No	No	Yes	No	No	No	Yes
Avoided risk of diagnostic review bias	NR	NR	NR	NR	No	NR	Yes	Yes	Yes	NR
Avoided risk of test review bias	NR	Yes	NR	NR	NR	NR	Yes	Yes	Yes	NR
Avoided risk of verification bias (all patients got conventional angiography)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Avoided risk of withdrawal bias (results reported for all patients)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No

NR, not reported in article

TABLE 42 *Carotid artery stenosis: articles satisfying inclusion criteria A–G*[105] *or A–F*[31,90,106–110]

	Sitzer, 1993[105]	**Remonda, 1998**[106]	**Korogi, 1994**[31]	**Ozaki, 1999**[107]	**Wilkerson, 1991**[108]	**Bianchi, 1995**[90]	**Drevet, 1997**[109]	**Riles, 1992**[110]
Time period	NR	NR	NR	NR	Feb. 1990–Jul. 1990	Jan. 1993–Jan. 1994	NR	Mar. 1989–Mar. 1990
Magnetic resonance technology	3D TOF, 1.5 T	3D contrast enhanced, 1.5 T	3D TOF, 1.5 T	3D TOF, 1.5 T	3D TOF, 1.5 T	2D TOF, 0.5 T	2D TOF, 0.5 T	2D TOF, 1.5 T
TR/TE/α	29/7/15	2.84/1.03/40	45/4.7/25 or 45/4.9/25 or 40/4.7/20 or 40/7/20	NR	50/14/50	60/16/50	42/8.4/55	NR
Imaging plane	Axial	Coronal	Axial	NR	Axial	Axial	Axial	?
NASCET method of measuring stenosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No. of patients	60	21	131	29	13	11	28	42
No. of vessels	120	44	251	54	26	21	56	75
% Male	72	81	47	NR	69	100	57	55
Age range (years)	39–80	53–83	6–77	NR	58–73	56–73	54–87	44–87
% Symptomatic	100	81	NR	< 100	77	64	82	NR
Further details on symptoms given in article	No	Yes	No	No	Yes	No	Yes	No
Avoided risk of diagnostic review bias	Yes	Yes	Yes	NR	Yes	NR	NR	Yes
Avoided risk of test review bias	Yes	Yes	Yes	NR	Yes	NR	NR	Yes
Avoided risk of verification bias (all patients got conventional angiography)	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Avoided risk of withdrawal bias (results reported for all patients)	Yes	Yes	Yes	No	Yes	No	No	Yes

TABLE 43 *Carotid artery stenosis: articles satisfying inclusion criteria A–E*[111–114] *or A–D*[115–119]*

	Currie, 1994[111]	**Anson, 1993**[112]	**Litt, 1991**[113]	**Polak, 1992**[114]	**Martinat, 1998**[115]	**Sardanelli, 1999**[116]	**Fellner, 1997**[117]	**Mattle, 1991**[118]	**Buijs, 1993**[119]
Time period	Apr. 1992–Oct. 1993	NR	Mar. 1989–Mar. 1990	NR	Feb.–Jul. 1997	NR	NR	May 1989–Jun. 1990	Jul. 1991–Mar. 1992
Magnetic resonance technology	3D TOF, 1.0 T	2D TOF, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T	3D contrast enhanced, 1.5 T	3D contrast enhanced, 3D TOF, 2D TOF, 1.5 T	3D TOF, (FISP and TONE), 2D TOF, 1.5 T	3D TOF, 1.5 T	2D TOF, 1.5 T
TR/TE/α	35/10/25	50/13–8.7/50	40–60/14–22/60–90	NR/NR/50	27/9/50	5/2/30 (contrast enhanced), 30/6/20 (3D TOF), 25/9/35 (2D TOF)	38/7/15 (FISP), 33/8/20 (TONE), 27/9/50 (2D TOF)	40/8/15 (bright blood), 1600/20/NR (black blood)	60/14/60
Imaging plane	?	Axial	Axial	Axial	Coronal	Contrast enhanced: axial and coronal TOF: axial	3D FISP: coronal 3D TONE and 2D TOF: axial	Sagittal	Axial
NASCET method of measuring stenosis	NR	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes
No. of patients	21	20	50	23	72	32	31	20	19
No. of vessels	42	40	100	46	54	60	47	39	NR
% Male	86	NR	56	57	NR	59	68	80	NR
Age range (years)	Median 63	NR	31–87	42–79	18–76	Mean 64.5	53–82	Mean 61	Mean 58
% Symptomatic	100	100	NR	57	NR	100	NR	65	95
Further details on symptoms given in article	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Avoided risk of diagnostic review bias	NR	Yes	Yes	NR	Yes	Yes	NR	NR	Yes
Avoided risk of test review bias	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
Avoided risk of verification bias (all patients got conventional angiography)	No	Yes	Yes	No	No	Yes	Yes	No	No
Avoided risk of withdrawal bias (results reported for all patients)	No	Yes	No	No	Yes	No	Yes	Yes	Yes

* *Further articles satisfying criteria A–D are listed in* Table 44

TABLE 44 *Carotid artery stenosis: further articles satisfying inclusion criteria A–D*

	Heiserman, 1992[120]	**Kido, 1991**[121]	**Nicholas, 1995**[122]	**Pavone, 1992**[123]	**Pavone, 1993**[124]	**Spartera, 1993**[125]	**Turnipseed, 1993**[21]	**Young, 1994**[23]
Time period	NR	NR	Aug. 1991–Dec. 1993	NR	NR	Jan. 1992–Dec. 1992	NR	Mar. 1992–Jan. 1993
Magnetic resonance technology	2D TOF, 1.5 T	2D TOF plus projection, 1.5 T	2D TOF, field strength not reported	2D TOF, 0.2 T	2D TOF, 0.2 T	2D TOF, 0.2 T	2D TOF and 2D phase contrast, 1.5 T	2D TOF and 3D TOF, 1.5 T
TR/TE/α	50/13–8.7/50	55/17/70	NR	60/10/90	60/10/90	NR	45/8.7/60 (2D TOF), 22/8.5/20 (2D phase contrast)	30/9/35 (2D TOF), 36/7/15 (3D TOF)
Imaging plane	Axial	Axial	NR	Axial	Axial	Axial	Axial	Axial
NASCET method of measuring stenosis	Yes	Yes	Yes	NR	NR	Yes	Yes	No*
No. of patients	41	41	40	31	42	51	30	79
No. of vessels	73	70	74	54	84	101	54	137
% Male	56	71	73	90	NR	NR	87	70
Age range (years)	17–84	48–85	49–85	43–76	32–82	NR	Mean 63	37–76
% Symptomatic	NR	NR	63	NR	NR	88	100	100
Further details on symptoms given in article	Yes	No	No	No	No	Yes	Yes	Yes
Avoided risk of diagnostic review bias	Yes	NR	Yes	NR	Yes	Yes	NR	Yes
Avoided risk of test review bias	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes
Avoided risk of verification bias (all patients got conventional angiography)	Yes	Yes	Yes	No	Yes	Yes	No	No
Avoided risk of withdrawal bias (results reported for all patients)	No	No	Yes	Yes	Yes	Yes	No	No

* *Diameter of common carotid artery used as denominator*

TABLE 45 *Peripheral vascular disease: five of the 20 articles satisfying all the inclusion criteria*

	Cortell, 1996[128]	**Laissy, 1998**[133]	**Meaney, 1999**[37]	**Perrier, 1998**[95]	**Quinn, 1997**[135]
Time period	Jun. 1993–Jul. 1994	May 1996–May 1997	NR	Mar. 1996–Mar. 1997	NR
Magnetic resonance technology	3D contrast enhanced TOF (above knee), 3D TOF, 1.5 T	2D contrast enhanced TOF, 1.0 T	3D contrast enhanced, 1.5 T	3D contrast enhanced, 1.5 T	2D TOF, contrast enhanced 3D TOF, 1.5 T
TR/TE/α	33/6.7/60	108/4/65	9.2/2.3/45	5 or 5.8/2 or 1.8/30–40	33/6.9/60 (2D TOF), 25/6.9/40 (3D TOF)
Imaging plane	Axial	Coronal–oblique	Coronal	? Coronal	Axial and coronal
No. of patients	31	20	20	23	53
No. of vessel segments	393	520	620	299	118
No. of normal segments included	NR	NR	NR	NR	78–81
Vessels	Popliteal, tibioperoneal, anterior tibial, peroneal, dorsal pedis, plantar arch	Femoral, popliteal, tibioperoneal trunk, tibial, peroneal	Distal aorta, iliac, femoral, popliteal, tibial, tibial peroneal trunk, peroneal	Iliac, femoral (above knee)	Iliacs
% Male	65	85	60	69	64
Age range (years)	42–85	42–62	47–83	50–87	42–92
% Symptomatic	100	100	100	100	100
Fontaine classification (%)	NR	NR	NR	I: 52 II: 22 III: 26	III: 100
Further details on symptoms given in article	Yes	Yes	Yes	No	No
Further details on future therapy given in article	No	No	No	No	No
Avoided risk of diagnostic review bias	Yes	Yes	Yes	Yes	Yes
Avoided risk of test review bias	Yes	Yes	Yes	Yes	Yes
Avoided risk of verification bias (all patients got conventional angiography)	Yes	Yes	Yes	Yes	No
Avoided risk of withdrawal bias (results reported for all patients)	Yes	Yes	Yes	No	Yes

TABLE 46 *Peripheral vascular disease: articles satisfying all the inclusion criteria*

	Rofsky, 1997[136]	**Sueyoshi, 1999**[139]	**Winterer, 1999**[140]	**Baumgartner, 1993**[93]	**Carpenter, 1994**[127]
Time period	Feb. 1996–Apr. 1996	NR	NR	NR	NR
Magnetic resonance technology	3D contrast enhanced, 1.5 T	3D contrast enhanced, 1.5 T	3D contrast enhanced, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T
TR/TE/α	5/2/30–50	9.8/1.4/20–30	6.2/1.9/30	55/16/60 (multislice), 35/12/60 (single slice)	NR
Imaging plane	Coronal	Coronal	Coronal	Axial	Axial
No. of patients	15	23	76	18	47
No. of vessel segments	150	423	1780	41	614
No. of normal segments included	NR	342	1163	0	202
Vessels	Abdominal aorta, iliac, femoral, popliteal, tibioperoneal trunk, tibial, peroneal	Iliac, femoral, popliteal, tibioperoneal trunk, tibial, peroneal	Aorta, iliac, femoral, popliteal, tibial, peroneal	Iliac, femoral	Aorta, iliac, femoral
% Male	60	87	57	72	53
Age range (years)	49–89	52–85	36–96	45–80	22–93
% Symptomatic	100	100	100	100	100
Fontaine classification (%)	NR	IIa or IIb: 83	NR	II: 89 III: 11	NR
Further details on symptoms given in article	No	Yes	Yes	No	Yes
Further details on future therapy given in article	No	No	No	No	Yes
Avoided risk of diagnostic review bias	NR	Yes	Yes	NR	Yes
Avoided risk of test review bias	NR	Yes	NR	Yes	Yes
Avoided risk of verification bias (all patients got conventional angiography)	Yes	Yes	Yes	Yes	Yes
Avoided risk of withdrawal bias (results reported for all patients)	No	Yes	Yes	Yes	Yes

TABLE 47 *Peripheral vascular disease: articles satisfying all the inclusion criteria*

	Davis, 1997[129]	**Eklof, 1998**[130]	**Ho, 1997**[131]	**Hoch, 1996**[82]	**Laissy, 1995**[132]
Time period	NR	Sep. 1994–Sep. 1995	NR	Feb. 1992–Jun. 1995	Mar. 1994–Nov. 1994
Magnetic resonance technology	2D-TOF, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T and 1.0 T	2D TOF, 1.0 T
TR/TE/α	33/3.9/60	41/9.1/60	1/15/6.8, 3/22.6/6.3	30–45/10/45, 30–45/6.9/60	32/8/50
Imaging plane	Axial	Axial	Axial	Axial	Axial
No. of patients	14	24	31	45	14
No. of vessel segments	154	168	169	352	56
No. of normal segments included	37	33	NR	NR	NR
Vessels	Tibial, peroneal, tibioperoneal trunk (below knee)	Popliteal, tibioperoneal trunk, tibial, peroneal, dorsal pedis, plantar arch (below knee)	Iliac, femoral (above knee)	Femoral, popliteal, tibial, peroneal, dorsal pedis (above and below knee)	Iliac (above knee)
% Male	43	50	58	76	86
Age range (years)	56–91	37–97	45–88	Mean 65	42–62
% Symptomatic	100	100	100	100	100
Fontaine classification (%)	IIa: 21 IIb: 50 III:29	NR	NR	NR	NR
Further details on symptoms given in article	Yes	Yes	Yes	Yes	No
Further details on future therapy given in article	Yes	No	No	Yes	Yes
Avoided risk of diagnostic review bias	Yes	Yes	Yes	Yes	Yes
Avoided risk of test review bias	Yes	Yes	Yes	Yes	Yes
Avoided risk of verification bias (all patients got conventional angiography)	Yes	No	No	Yes	Yes
Avoided risk of withdrawal bias (results reported for all patients)	Yes	Yes	Yes	Yes	No

TABLE 48 *Peripheral vascular disease: articles satisfying all the inclusion criteria*

	Mulligan, 1991[134]	**Snidow, 1995**[137]	**Steffens, 1997**[138]	**Timonina, 1999**[92]	**Yucel, 1993**[141]
Time period	Jul. 1989–Mar. 1990	NR	Mar. 1995–Oct. 1995	NR	Feb. 1992–Sep. 1992
Magnetic resonance technology	2D TOF, 1.5 T	2D TOF, 1.5 T	2D phase contrast, 1.5 T	2D TOF, 1.5 T	2D TOF, 1.5 T
TR/TE/α	50/16/90	35/8/35	83/9/11	29/6.7/40	29/6.7/45–60
Imaging plane	Axial	Axial	Axial	Axial	Axial
No. of patients	12	42	115	22	25
No. of vessel segments	140	378	253	220	206
No. of normal segments included	81	NR	0	NR	0
Vessels	Distal aorta, iliac, femoral, popliteal	Iliac, femoral, popliteal, tibioperoneal trunk, tibial, peroneal	Aortic bifurcation, iliac, femoral, popliteal	Aorta, iliac, femoral arteries (above knee)	Distal abdominal aorta, iliac, femoral, popliteal
% Male	100	95	NR	100	60
Age range (years)	53–72	NR	32–81	32–64	37–80
% Symptomatic	100	100	100	100	100
Fontaine classification (%)	NR	NR	NR	NR	NR
Further details on symptoms given in article	No	No	Yes	Yes	Yes
Further details on future therapy given in article	No	No	No	No	No
Avoided risk of diagnostic review bias	NR	Yes	Yes	NR	Yes
Avoided risk of test review bias	No	Yes	Yes	NR	Yes
Avoided risk of verification bias (all patients got conventional angiography)	Yes	Yes	Yes	No	Yes
Avoided risk of withdrawal bias (results reported for all patients)	Yes	Yes	Yes	Yes	Yes

Appendix 5

Definitions

TP Number of positive cases correctly identified as positive by test
FP Number of negative cases incorrectly identified as positive by test
FN Number of positive cases incorrectly identified as negative by test
TN Number of negative cases correctly identified as negative by test

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN + FP)
Positive predictive value = TP/(TP + FP)
Negative predictive value = TN/(FN + TN)
Accuracy = (TP + TN)/(TP + FP + FN + TN)

LR+ Likelihood ratio of a positive test result ('A positive test result is about LR+ times more likely in someone with the condition than in someone without it'):

LR+ = sensitivity/(1 – specificity)

LR– Likelihood ratio of a negative test result ('A negative test result is about LR– times more likely in someone without the condition than in someone with it'):

LR– = (1 – sensitivity)/specificity

Prevalence = pretest probability
= (TP + FN)/(TP + FP + FN + TN)
Diagnostic odds ratio = (TP × TN)/(FP × FN)
= (sensitivity × specificity)/
[(1 – specificity)
(1 – sensitivity)]

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